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126	6	*for* " 272° " *read* " 227° ".
126	7 *	*for* " pyridoacridine " *read* " pyridoacridone ". In the Table of Contents of the June *Journal*, paper 172, *for* " Esters of carbonic acid " *read* " Esters of carbamic acid ".
1263	28—29	*for* " (XII; R = H) " *read* " (XII) ".
1602	34	*for* " chromate " *read* " chromite ".

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(*b*) *British Abstracts*.—The Society collaborates with the Society of Chemical Industry, the Physiological Society, the Biochemical Society, and other organisations in contributing to the maintenance of the Bureau of Abstracts, which issues every month abstracts of papers dealing with all branches of pure and applied chemistry, physiology and anatomy published in all parts of the world.

British Abstracts A is divided into three sections: AI, General, Physical, and Inorganic Chemistry; AII, Organic Chemistry; AIII, Physiology and Biochemistry, including Anatomy.

(*c*) *Annual Reports on the Progress of Chemistry*.—These reports, written by experts, summarise the important new advances in pure chemistry and related subjects.

(*d*) *Quarterly Reviews* are composed of articles on selected topics from the whole field of chemistry.

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Books available on loan may be sent by post to Fellows residing in Great Britain or Ireland.

MEETINGS

(*a*) *In London*.—Scientific Meetings of the Society are held usually on the first and third Thursdays of each month from October to June at Burlington House, at which papers dealing with original work are read and discussed, organised discussions on subjects of current interest are arranged, and lectures by eminent British and foreign chemists are delivered.

(*b*) *Outside London*.—Scientific Meetings and lectures arranged by the Society's Local Representatives are also held outside London, and form an important part of the activities of the Society.

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A Research Fund is available for the assistance of chemical research, and sums amounting annually to about £700 are granted for this purpose. Application for grants must be made on the appropriate form, which may be obtained from the General Secretary.

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4. Any paper describing work done under a Government Department or similar body must be accompanied, when necessary, by a written authority approving the submission of the paper for publication in the *Journal*.

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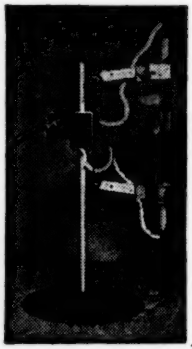

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The majority of the monographs bear the same titles as in previous years. Newcomers are "The Protein Fibres" and "Pest Control in Agriculture". The sections devoted to "Plastics" and "Resins, Drying Oils, Varnishes and Paints" have been contributed respectively by the Plastics Group, and the Oil and Colour Chemists Association.

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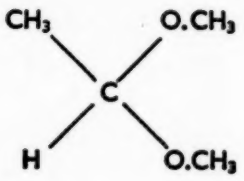

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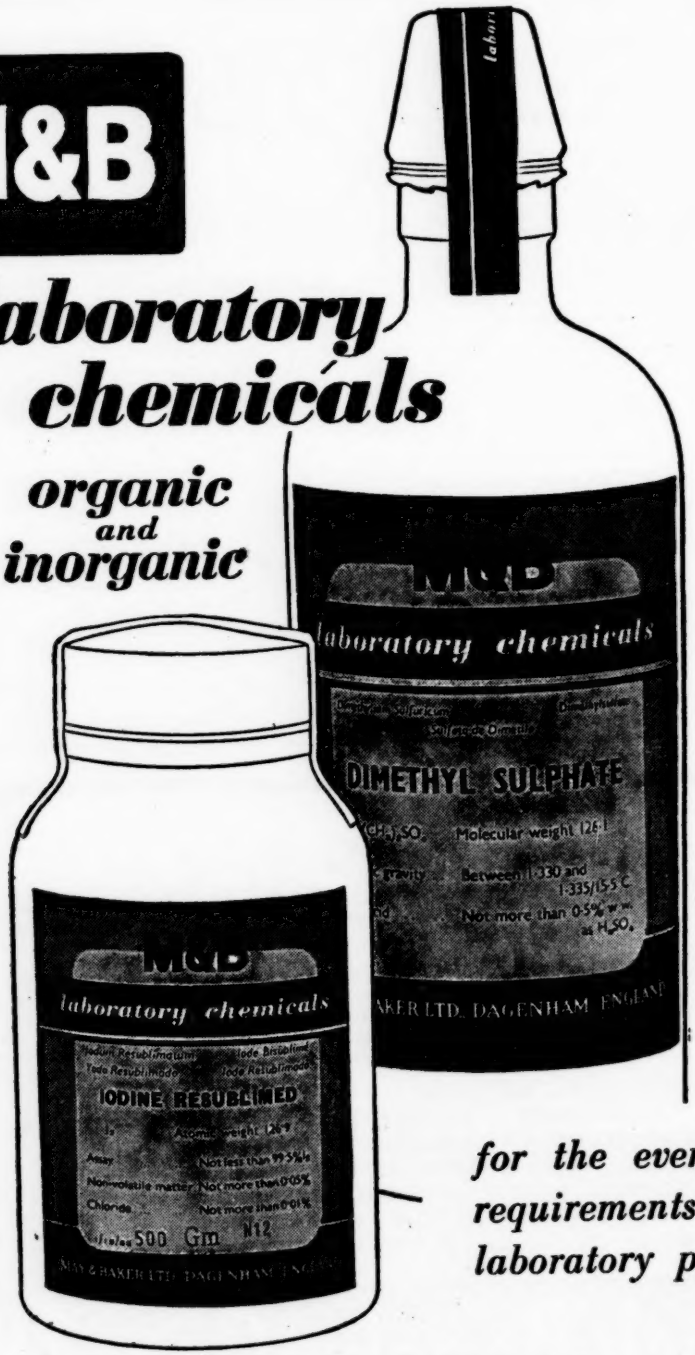

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bound to state that there exists a great deal of scepticism and doubt concerning many, if not all, of his claims. The general expert opinion may, perhaps, be summed up in the verdict " not proven ". In this connection may be cited the recent important book on " Photosynthesis " by E. I. Rabinowitch (Interscience Publishers Inc., New York, 1945), in which very many of the results claimed by Baly are strongly criticised in a detailed manner. On page 87 of this book it is stated that " practically all attempts to repeat Baly's experiments elsewhere have given negative results ". I understand that the criticisms of Rabinowitch are considered in the United States to be fair and just, and I think I am justified in stating that at least two eminent organic chemists in Great Britain share a good deal of his scepticism. It would seem that Baly was carried away by his enthusiasm and that his early results, incorrectly interpreted, apparently led to a veritable obsession which affected self-criticism and correct judgment. However that may be, he made a mighty effort to establish the existence of photosynthesis in inanimate systems, and, although the results he obtained appear to be still in dispute, it is quite possible that future and undisputable success may owe much to the stimulus derived from his investigations in this difficult field.

In concluding the account of Baly's scientific activities, it is possible only to make a brief reference to published work in various other fields of research, *e.g.*, the co-precipitation of sewage colloids with fine suspensates, the properties of sewage colloids, the mechanism of the activated sludge process of sewage disposal, the adsorption of the hydrous metallic oxides by kieselguhr, the reactivity of ammonia, the occurrence of helium and neon in vacuum tubes, high energy chemistry and vitamins, the kinetics of photosynthesis, the adsorption of gases and the equation of the liquid state, and the selective photochemical action of polarised light. As secretary to the British Association Committee entrusted with reports on absorption spectra, Baly was responsible for four valuable reports, published in 1916, 1920, 1922, and 1928. In 1928 he was President of Section B at the meeting of the British Association in Glasgow, his Presidential Address dealing with " Phosphorescence, Fluorescence, and Chemical Reaction ". For a number of years he published reviews of the progress of inorganic chemistry in the *Annual Reports*.

Baly went with the British Association to Canada (1924), South Africa (1927), and India (1937). After the meeting in Canada he undertook an extensive lecture tour in the United States. On the occasion of the Indian visit he received the honorary degree of D.Sc. of the University of Benares. Under the expert tuition of J. N. Collie he became a good rock climber, doing many climbs in Skye (some of which were new), and becoming a member of the Scottish Mountaineering Club. During his time as Professor at Liverpool he took an active part in the work of the Liverpool Section of the Society of Chemical Industry, becoming Chairman of the Section and at the same time a member of Council of the Society. He was elected an honorary member of the Society of Dyers and Colourists, to the West Riding Section of which he gave an annual lecture for 26 years.

Baly was an active and forceful person who made his influence felt in any society. Besides his knowledge of, and skill in, music, he was a most lively conversationalist, and one who understood and enjoyed the good things of life. His cheerful and optimistic temperament could enliven any company and endeared him to a host of friends. Self-confidence is a necessary virtue in life, and one may, perhaps, say (without any ill-feeling) that he was richly endowed with this virtue. Science cannot advance without the formation of hypotheses, and Baly possessed in good measure this important gift of imagination. It may be possible that, if he had a fault, it was due to the fact that his optimistic and self-confident mind could not always sufficiently control the wealth of his imagination. He was most certainly a highly skilled and resourceful experimenter. He was also a source of inspiration to many generations of research students and collaborators, who were strongly influenced by his immense energy and the activity of his mind.

F. G. Donnan.

DOROTHY JORDAN LLOYD.*

1889—1946.

Dorothy Jordan Lloyd was born on May 1st, 1889, the daughter and grand-daughter of two prominent surgeons in Birmingham. It would appear natural that her early studies at Newnham were in zoology, passing over to physiological and then physicochemical studies of muscle. During the First World War, her scientific pursuits were diversified, and under the auspices of

* Reprinted by permission from *Nature*, 1947, **159**, 190.

the Medical Research Committee she was one of a team who studied substitutes for components of culture media for bacteria which were then in short supply. Then her brilliant short paper on the causes and prevention of ropiness in bread was most appropriate to war-time, and indicated the versatility of her mind. Under the stimulating influences of Gowland Hopkins and particularly of W. B. Hardy, she was led to the long-sustained studies of swelling in colloidal systems, which when carried over to the "structured" proteins in animal skins gained for her the firmly established international reputation as the authority on the chemistry of leather which she held at her death on November 21st, 1946. Thus, zoology in Part II of the Tripos, research in physiology followed by the D.Sc.(London), after some interval the Fellowship of the Institute of Chemistry in 1922, authorship of a standard work, "Chemistry of the Proteins" (first edit., 1926; second, with Ann Shore, 1938), and the directorship of the British Leather Manufacturers' Research Association (1927—1946) are the signposts of an exceptional career.

The output of Dr. Jordan Lloyd's published work both in pure and applied chemistry is impressive. Returning after the First World War to her main line of research, she published her earliest papers on the swelling of gelatin under the auspices of the Medical Research Committee; but most of her work on this subject, and indeed by far the greater part of her scientific publications, was published after she joined the staff of the British Leather Manufacturers' Research Association in 1921. Her early work followed on that of Procter by establishing the swelling curves of gelatin as affected by hydrogen-ion concentration and demonstrating the effect of salts on the swelling. Later she showed how lyotropic effects are superimposed on the swelling effects of the Gibbs–Donnan theory, and illustrated the temperature effects which that theory predicts. She emphasized the importance of the balance between osmotic pressure and cohesion in controlling the degree of swelling. This work was extended to a study of the swelling of protein fibres (collagen, silk, hair) in aqueous systems, in which not only the water uptake but also the changes in length and thickness of the fibres were followed; these changes are of importance in giving a more detailed picture of the effects of swelling on the individual fibres and on the interwoven structure of hides. These studies of fibres showed the effect of hydrogen-ion concentration on swelling, in so far as it produces salt formation by the protein, and also illustrated certain lyotropic effects. The weakening of the structure of the fibres which was observed in certain conditions was linked with the study of the molecular structure of fibrous proteins.

A number of Dr. Jordan Lloyd's papers deal with the closely related subjects of the chemical make-up of the fibrous proteins, and its bearing on their structure, water relationships, and swelling properties. She carried out experiments on the amount of water in gelatin which is "bound", that is, associated with specific groups in the protein molecules, and is to a considerable extent independent of osmotic effects. In addition to these studies of the molecular structure of fibrous proteins, she investigated the fibrous structure of hides and skins, and showed how the swelling properties of collagen fibres are affected by the sheath or network ("reticulin") which surrounds them and can be broken by strong swelling or weakened at very low and very high pH values.

The above work dealt with proteins in aqueous systems. In later developments Dr. Jordan Lloyd turned to a study of the effects of non-aqueous liquids (organic solvents and acids), using changes in volume, dimensions, and extensibility of fibrous proteins in these liquids, to throw light on the nature of the cross-bonds which hold the protein molecules to one another, and on the orientation of these molecules in the fibres.

Her keen sense of the applicability of this mass of scientific results to the processes of the industry was coupled with a resolution and an unfailing affability towards industrialists and their technicians which was an immense advantage to the Research Association. The long series of her lectures, well attended by its members and their technical personnel, and based on the work in progress in the Association's laboratories, were symptomatic of her hold on the imaginations of those in the industry, and illustrated her wide grasp of the application of science to it. In the industry the measurement of hydrogen-ion concentration and buffer index became usual, particularly in heavy-leather tanning; the use of the microscope and the correlation of photomicrographs with composition and use of tan liquors led to control of quality in leather in general and also in its production for special purposes—a control not hitherto attained; the disposition of the tanned fibres in leather is now related to its various measurable physical properties, and hence to quality and serviceability—such have been developed largely by her leadership and enthusiasm, which have contributed much to the gradual change of leather production from a chancy industrial art to a sequence of processes scientifically controlled.

Miss Jordan Lloyd was perhaps unique among the scientific women of her time—a vigorous

and vivacious leader of her mixed team both in triumph and tribulation (for her laboratories were twice wrecked in the "blitz" on Bermondsey); a clear thinker and good speaker with a constructive mind; a manager with ability to delegate; a research worker herself who displayed an arresting interest in the investigations of many others; and with a demeanour and practical outlook in the tanneries which appealed to the employers and their technicians. She can have perhaps no more fitting epitaph—and one possibly no more welcome to her—than the impressive volumes now appearing which describe the results of twenty-five years of research for the British leather industry by the British Leather Manufacturers' Research Association under her inspiring leadership.

ROBERT H. PICKARD.

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351. *Properties of Some Simple Oxides and Spinels at High Temperatures.*

By D. J. M. BEVAN, J. P. SHELTON, and J. S. ANDERSON.

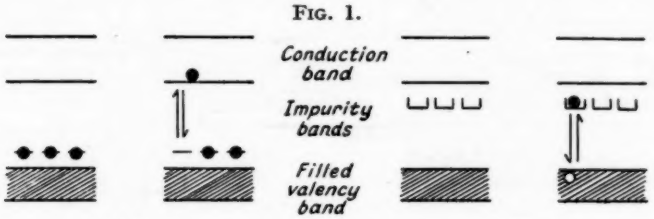
The electrical conductivity of the solid oxides ZnO, Fe_2O_3, Cr_2O_3, $ZnFe_2O_4$, $ZnCr_2O_4$, $MgFe_2O_4$, and $MgCr_2O_4$ has been determined at temperatures up to 1000°. Measurements in different gaseous atmospheres (air or oxygen, vacuum, hydrogen, or carbon monoxide) show that, as expected from general principles, ZnO, Fe_2O_3, $ZnFe_2O_4$, and $MgFe_2O_4$ are metal-excess (electron) conductors; Cr_2O_3 is an oxygen-excess or metal deficiency (positive hole) conductor. Zinc and magnesium chromites, potentially amphoteric, display positive hole conduction only.

The conductivity in each case responds reversibly to changes in oxygen pressure at temperatures below $0{\cdot}5T_m$ but above about $0{\cdot}25T_m$ (T_m = m. p. in ° K.), showing that impurity semiconduction can originate from the production of lattice defects in surface atom layers only. $ZnCr_2O_4$ at high temperatures shows evidence of changes in the concentration of a built-in stoicheiometric excess of oxygen in the air-sintered material. $ZnCr_2O_4$ formed by reaction of ZnO and Cr_2O_3 in hydrogen is a very poor conductor.

Three roughly defined ranges of temperature can be recognised as determining the properties of solid oxides. (A) A high-temperature range, in which self-diffusion permits of attainment of true thermodynamic equilibrium. (B) An intermediate range, in which lattice equilibrium is frozen, but surface mobility is manifest. (C) Temperatures too low for equilibration of the surface, all properties varying non-reproducibly. Semiconducting properties behave reversibly over temperature ranges A and B. The primary processes of chemical reaction by solid oxides involve (i) chemisorptive equilibrium of oxygen (or reducing gases) with fully tenanted or partially stripped crystal lattice surfaces, and (ii) diffusion processes whereby lattice defects migrate into the interior of the crystal lattice. The second stage can occur only in temperature range A.

ACCORDING to the statistical thermodynamic model of solids (Schottky and Wagner, *Z. physikal. Chem.*, 1930, *B*, **11**, 165), an equilibrium must be set up, at temperatures where diffusion permits, between a solid metallic oxide and oxygen, present at a certain partial pressure in the surrounding

FIG. 1.



gas phase. Any change in the partial pressure of oxygen should, theoretically, lead to changes—even if analytically indetectable—in the composition of the solid oxide, the direction of departure from the ideal composition depending upon the valency properties of the cations. For oxides derived from the highest valency state of a metal (*e.g.*, ZnO), the ideal formula represents an upper limiting composition. By loss of oxygen from the ideal crystal, an oxide is formed with an excess of metal atoms (*i.e.*, of Zn^{2+} cations + 2 electrons each); the excess electrons are trapped in the neighbourhood of an interstitial Zn^{2+} cation, or of a vacant anion site. In terms of the band theory of solids, such supernumerary metal atoms constitute filled impurity levels in the energy scheme of the crystal lattice, the distribution of electrons between the impurity levels and the conduction band being governed by a Boltzmann distribution (Fig. 1A). Similarly, for oxides derived from the lower of two valency states, the stoicheiometric

compound should represent a lower limiting composition; with increasing oxygen pressure, additional O^{2-} ions may be built on to the crystal lattice, electrons being withdrawn in corresponding number from cations which are thereby converted into cations of higher valency. These constitute empty impurity levels, or trapped positive holes; a temperature-dependent concentration of mobile positive holes results from the Boltzmann distribution of electrons between these levels and the filled valency band of the cations (Fig. 1B).

The conductivity of oxides at high temperatures thus depends upon the oxygen pressure in a manner which reflects the mechanism of conduction, and provides an extremely sensitive index of deviations from stoicheiometric composition. For simple oxides the dependence of conductivity upon oxygen pressure should evidently be predictable (Friederich, *Z. Physik*, 1925, **31**, 813; Meyer, *ibid.*, 1933, **85**, 278); some double oxides, *e.g.*, the chromite spinels, such as $ZnCr_2O_4$, might *a priori* be of the type designated by Schottky as amphoteric conductors, giving rise to impurity conduction of either kind. As is shown below, $ZnCr_2O_4$ and $MgCr_2O_4$ are, in fact, positive hole conductors under all conditions.

There is already an extensive literature relating to the conductivity of certain metallic oxides. In adding to this it has been our intention to elucidate further the nature of the equilibrium established between a solid oxide and the gas phase, and, in particular, the processes whereby equilibrium is established. The results may be correlated, not only with the theoretical model, but also with the considerable body of information amassed during recent years on the phenomenology of reactions involving solids.

Experimental.

Measurements of conductivity were made potentiometrically on sintered, compressed plates of the oxides. Jander and Stamm (*Z. anorg. Chem.*, 1930, **199**, 165) showed that the ionic contribution to the

Fig. 2.

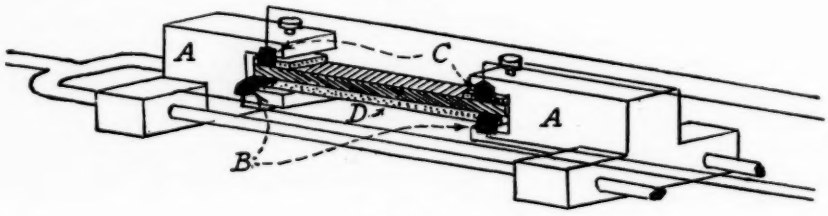
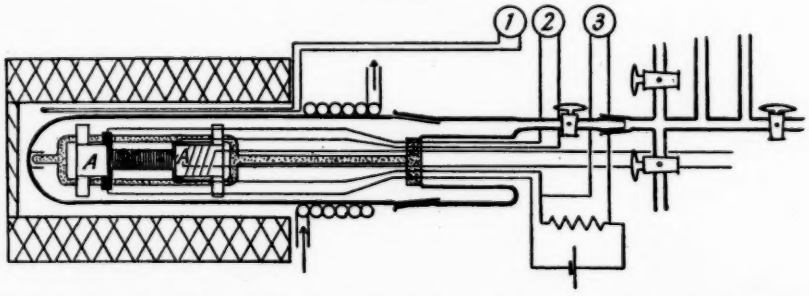


Fig. 3.



conductivity of a number of typical oxides and spinels, is, at the most, very small, so that direct current measurements are permissible. The specimens were made by compressing the individual oxides, or the reacted spinels, in a hardened steel die under a pressure of 5—10 tons per square inch, to form plates 25 mm. × 5 mm. × 1—1·5 mm. thick. Plates so obtained were, in most cases, very fragile and troublesome to handle; when they were heated at temperatures above the Tammann point (*e.g.*, to 1000—1050°, for 4—12 hours) the particles fritted together to give plates of excellent mechanical strength. Alternatively, the unreacted oxide mixtures were pelleted and then heated at 1000—1050°. The processes of reaction and fritting then proceeded concurrently, forming compact, hard plates.

The plates were mounted between electrode holders (*A*, *A*, Figs. 2, 3) of heat-resistant steel (25% Cr, 20% Ni), supported by a silica-rod framework. Silica slips *D*, which served also as insulators, clamped the plates firmly in contact with two platinum-foil electrodes (*B*, *C*) at each end, one on either face; these served as current leads and potential leads respectively. The specimen, in its electrode assembly, was fitted through a silica-to-Pyrex standard ground joint into a silica jacket. The jacket was connected to vacuum pumps, manometer, McLeod gauge, and reservoirs for air, hydrogen, or carbon monoxide (Fig. 3).

Materials.—Zinc oxide. This was prepared by heating zinc oxalate at 550° (Rosencranz, *Z. physikal. Chem.*, 1931, *B*, **14**, 407).

Magnesium oxide. Magnesium hydroxide was precipitated from magnesium nitrate solution by means of a slight excess of sodium hydroxide. The precipitate was repeatedly washed by decantation with a large volume of water, dried at 110°, and ignited for 2 hrs. at 500°. According to Fricke and Lüke (*Z. Elektrochem.*, 1935, **41**, 174) the oxide so obtained is in a highly reactive state.

Ferric oxide. Amorphous ferric hydroxide was precipitated, by means of silica-free ammonia, from a solution made by oxidising A.R. ferrous sulphate with bromine. After prolonged washing by decantation, the precipitate was ignited at 450° for 3 hrs. The product is α-Fe_2O_3 in a reactive state (Fricke and Ackermann, *ibid.*, 1934, **40**, 630).

Chromic oxide. Chromic anhydride was dried at 150° (2 hrs.) in a current of dry, filtered air. The temperature was raised to 350° (2 hrs.) and ultimately to 450° (3 hrs.). The product was a very fine, dark green powder.

All materials were of A.R. quality, and distilled water was used throughout. The washing of precipitates was, in every case, prolonged for some time after the last detectable traces of electrolytes had been removed. After ignition, the oxides were very hygroscopic, and were stored in a desiccator over phosphoric oxide.

Mixtures of $ZnO + Fe_2O_3$, $MgO + Fe_2O_3$, $ZnO + Cr_2O_3$, $MgO + Cr_2O_3$ were made up in exactly stoicheiometric ratio, allowing for the ignition loss of the components. The oxides were intimately mixed by tumbling and grinding. It has been shown by various workers (Hüttig, Schröder, etc.) that spinel formation from ferric oxide proceeds freely above about 720°, the Tammann temperature of ferric oxide, at which the requisite freedom of diffusion of Fe^{3+} cations becomes appreciable. The reaction temperature of chromic oxide in air is rather lower. The oxide mixtures were, in general, submitted to reaction at 1050° for 24 hrs.; under these conditions reaction was substantially complete, as was verified analytically for several samples.

General Procedure.—The conductivity of each material was measured over a wide range of temperature, extending in each case above the Tammann temperature ($= 0{\cdot}5T_m$, where T_m = m. p. in ° K.), since only above this temperature is the speed of self-diffusion enough to establish true equilibrium of lattice defects. Oxygen pressure was varied by measurement in oxygen (1 atm.), in air at the atmospheric or reduced pressures down to 10^{-3} to 10^{-4} mm., or in hyrodgen or carbon monoxide to establish very low effective partial pressures of oxygen.

Results and Discussion.

For all the substances studied, the conductivity $\kappa(T)$ (at T° K.) conforms to the usual law

$$\kappa(T) = Ae^{-E/kT} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

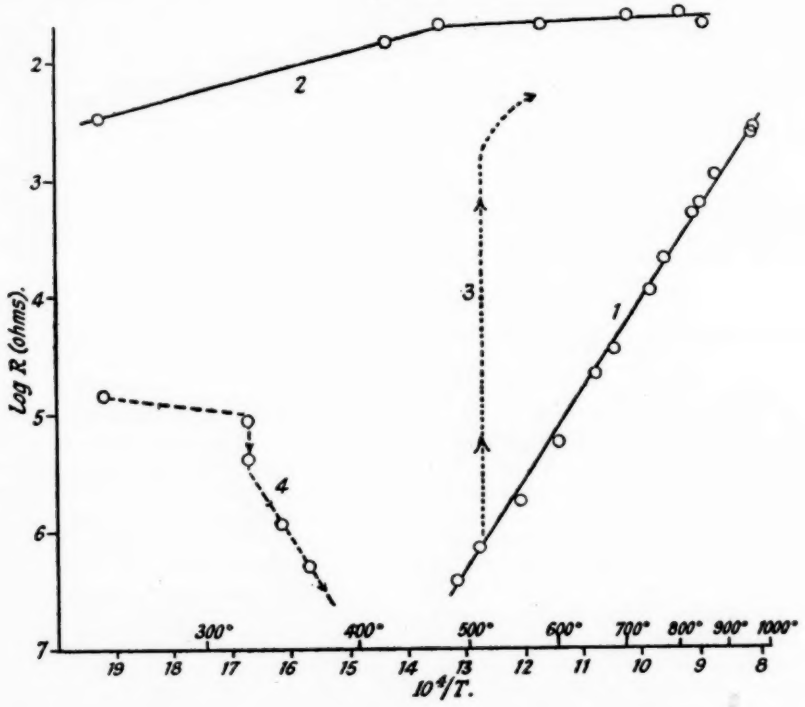
where A, involving the number of potentially conducting centres (and hence the stoicheiometric excess of metal or oxygen) and the mean free path of the conductivity electrons, is practically independent of the temperature, and E is an energy increment which determines the Boltzmann distribution of electrons between the impurity levels and the energy bands of the crystal. The effect of changes in partial pressure of oxygen is to control the concentration of impurity levels. Absolute values of $\kappa(T)$ have little significance, since the conducting cross section of a fritted granular material is very indeterminate and the contribution made by surface conduction (cf. Dubar, *Ann. Physique*, 1938, **9**, 5) is unknown. Through these and other factors, the values of κ found for semiconductors are notoriously dependent on past thermal history and structural factors. Nevertheless, results obtained for duplicate plates prepared from the same samples of oxide were satisfactorily reproducible, as the appended curves show.

Zinc Oxide.—Measurements on zinc oxide at high temperatures have been made previously by Jander and Stamm (*loc. cit.*), von Baumbach and Wagner (*Z. physikal. Chem.*, 1933, *B*, **22**, 199) and Miller (*Physical Rev.*, 1941, **60**, 890). As expected from the Friederich–Meyer rule, and as verified by von Baumbach and Wagner, the conductivity is greatly enhanced at low pressures of oxygen (cf. curves 1 and 2, Fig. 4), the enhancement being truly reversible at high temperatures. Von Baumbach and Wagner adduced sound evidence that the augmented conductivity could not be attributed to the formation of free zinc, and they considered that the variation of κ with oxygen pressure, between 10 and 760 mm. of oxygen, and at one temperature (650°) agreed with Wagner's model for non-stoicheiometric conducting solids (*Z. physikal. Chem.*, 1933, *B*, **22**, 181), which leads to the relation $\log \kappa = B - \frac{1}{6} \log p_{O_2}$. However, two assumptions are implicit in Wagner's model: (*a*) that changes in conductivity arise solely from changes in the temperature-independent factor A of equation (1), this being taken as directly proportional to the concentration of excess metal atoms; (*b*) that one can ignore the surface, assuming that true equilibrium is attained within a crystal lattice of infinite extent.

Our results, over a wider range of oxygen pressure, and at temperatures between 470° and 1000°, show clearly, however, that the energy increment E of the conduction process changes greatly [curve 2, p_{O_2} about 10^{-4} mm., $E = 0{\cdot}038$ e.v., $\kappa(600°) = 0{\cdot}51$; curve 1, $p_{O_2} = 150$ mm., $E = 1{\cdot}60$ e.v., $\kappa(600°) = 1{\cdot}5 \times 10^{-4}$], the profound change in conductivity arising principally from this factor. The detailed relation between the conductivity of zinc oxide and the oxygen

pressure is of some theoretical interest and importance, and will be dealt with in a later paper. Fig. 4 accordingly represents results relating to the two extreme conditions only. The incorrectness of the second assumption is discussed below, in relation to the results obtained with other oxides. We may here draw attention to curve 3, representing the slow, progressive rise of conductivity of a zinc oxide plate at 500° when the oxygen pressure was reduced from 150 to 10^{-4} mm. Response to any change of oxygen pressure, and attainment of equilibrium with the environment, was not achieved at temperatures much lower than 500°; at high temperatures, change of resistance on evacuation or on admission of oxygen was immediate. The melting point of zinc oxide is probably about 2000° (Hüttig and Toischer, *Z. anorg. Chem.*, 1932, **207**, 273), so that processes involving self-diffusion through the crystal lattice can hardly be important below about 860°. The inference is clear that at 500°, at least, the process which gives rise to the highly conducting state can only involve the superficial layers of atoms of the crystalline particles.

FIG. 4.



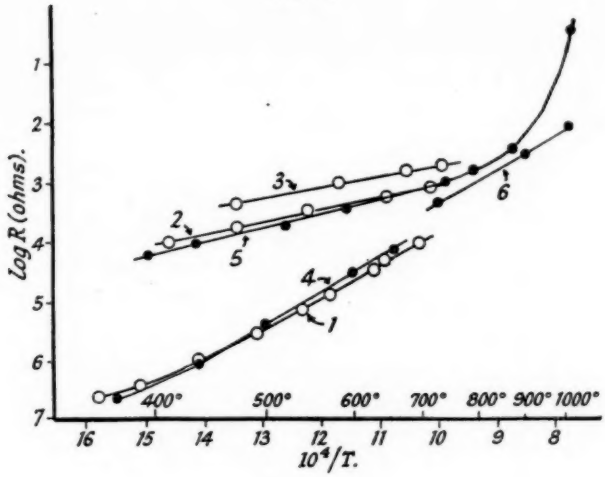
It may be noted, further, that in none of our experiments with zinc oxide prepared from zinc oxalate did we obtain the inflexion of curvature of the conductivity–temperature curve found by Jander and Stamm, von Baumbach and Wagner, and Miller. Von Baumbach and Wagner state that the measurements were reproducible with both ascending and descending temperatures. As the inflexion was found at temperatures where diffusion processes may just become important, it may possibly involve some factor connected with the interplay of surface and bulk processes, in respect of which our " active " zinc oxide differed from the zinc oxides of unspecified history used by the other workers.

Ferric Oxide.—Results for two plates are summarised in Fig. 5. Variation of conductivity with oxygen pressure shows that, as would be expected, ferric oxide is a metal-excess conductor. No drift of conductivity occurred on prolonged heating in a vacuum at 730°, as would have been the case if magnetite had been formed as a new phase (cf. plate 2). A second plate, similarly treated in air (curve 4) and in vacuum (curve 5) behaved similarly, but on raising the temperature to 1000°, formation of magnetite in continually increasing amount was shown by a rapid 100-fold rise in the conductivity; reversal of this dissociation, on admission of air, is shown by curve 6.

Wagner and Koch (*Z. physikal. Chem.*, 1936, *B*, **32**, 439) measured the conductivity of

ferric oxide at 1000° only, and concluded that it was independent of the oxygen pressure. As may be seen from Fig. 5, curves 1 and 2, 4 and 5 would, in fact, intersect rather above 1000°, so that at that temperature the effect of reducing the oxygen pressure would be but small. The inference that ferric oxide is an intrinsic semiconductor is, therefore, unjustified, being based upon inadequate experimental material. It is, however, surprising that Wagner and Koch did not observe any thermal decomposition of the ferric oxide at that temperature.

FIG. 5.



Fe_2O_3.

Plate 1. Heated in air to 702°. Curve 1 : $E = 1{\cdot}06$ e.v., $\kappa(600°) = 5{\cdot}5 \times 10^{-4}$
Evacuated at 700° to 10^{-3} mm. Curve 2 : 0·38 e.v. $9{\cdot}7 \times 10^{-3}$
Evacuated at 410° to 10^{-5} mm. Curve 3 : 0·38 e.v. $2{\cdot}4 \times 10^{-2}$

In accord with the melting point of ferric oxide (*ca.* 1570° c.), processes of reaction, etc., which depend on self-diffusion are imperceptible below 650°, and become rapid above 700°. The conductivity of ferric oxide responds to changes in oxygen pressure at 410°, whereas formation of magnetite—a process involving the diffusion of cations through the crystal lattice—was observed only at temperatures well above 720°.

Our observations have some bearing on the problem of the mutual miscibility of α-ferric oxide and magnetite. Sosman and Hostetter (*J. Amer. Chem. Soc.*, 1916, **38**, 807) and, later, White (*Iron and Steel Inst.*, Carnegie Schol. Mem., 1938, **27**, 1) concluded from tensimetric evidence that between 1100° and 1450° the $\overline{Fe_2O_3}$ and $\overline{Fe_3O_4}$ phases each had a fairly wide range of existence. Sosman's later work (Greig, Posnjak, Merwin, and Sosman, *Amer. J. Sci.*, 1935, **30**, 239) indicated, however, that when true equilibrium was attained by proper annealing, the degree of mutual solid solution of the two oxides was extremely small. Conductivity measurements are extremely sensitive to the formation of the highly conducting magnetite as a second phase, and to the growth of the amount of magnetite. Our observations strongly suggested that magnetite was formed as a separate phase when a very small stoicheiometric proportion of oxygen had been removed from the ferric oxide; although not conclusive, this would be in accord with the work of Greig, Posnjak, Merwin, and Sosman.

Chromic Oxide.—The conductivity of chromic oxide has apparently not been recorded previously, but the relative stabilities of the valency states of chromium indicate that the oxide should be an oxygen-excess (positive hole) conductor. This is confirmed by the results summarised in Fig. 6.

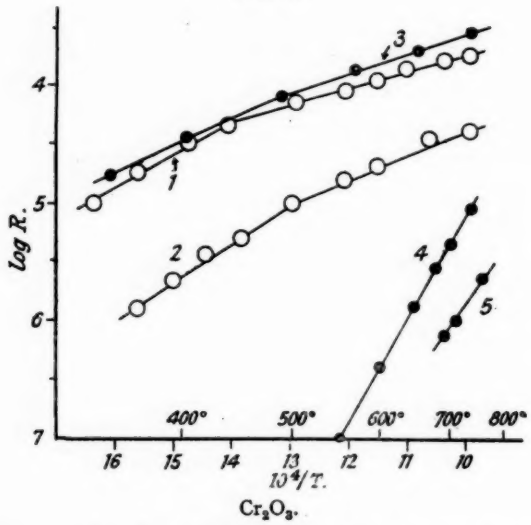
Curve 1 [$E = 0{\cdot}60$ e.v., below 450°; $E = 0{\cdot}30$ e.v., $\kappa(600°) = 3{\cdot}7 \times 10^{-3}$ at higher temps.] represents the conductivity of plate 1 in air; curve 2 [$E = 0{\cdot}67$ e.v., below 500°; $E = 0{\cdot}50$ e.v., $\kappa(600°) = 7{\cdot}4 \times 10^{-4}$ at higher temps.] that obtained when the oxygen pressure was reduced (at 740°) to about 10^{-3} mm. The decrease in conductivity corresponds to a decrease in the stoicheiometric excess of oxygen, and consequent conversion of higher-valent chromium cations into Cr^{3+} cations. Much lower effective partial pressures of oxygen are obtainable by admission

of hydrogen or carbon monoxide; these do, in fact, lower the conductivity still further. Thus, at 740°, the resistance of plate 1 in different gaseous atmospheres varied successively as follows:

In air (p_{O_2} = 150 mm.)	$5{\cdot}2 \times 10^3$ ohms.
In vacuum (p_{O_2} about 10^{-3} mm.)	$2{\cdot}5 \times 10^4$,,
In 2 cm. electrolytic hydrogen (0·1% O_2, *i.e.*, ultimate $p_{H_2} : p_{H_2O}$ = about 500)	$3{\cdot}0 \times 10^5$,,
In 10 cm. electrolytic hydrogen	$9{\cdot}5 \times 10^5$,,
In 70 cm. oxygen	$5{\cdot}2 \times 10^3$,,
In 3 cm. carbon monoxide	$8{\cdot}0 \times 10^5$,,

The conductivity of " reduced " chromic oxide was more fully investigated on a second specimen (conductivity in air, curve 3), for which the conductivity curves in 2-cm. pressure of carbon monoxide, admitted at 740° [curve 4, $E = 1{\cdot}79$ e.v., $\kappa(600°) = 1{\cdot}26 \times 10^{-3}$] and in 20 cm. of hydrogen [curve 5, $E = 1{\cdot}38$ e.v., $\kappa(600°) = 4{\cdot}4 \times 10^{-3}$] are shown in Fig. 6.

FIG. 6.



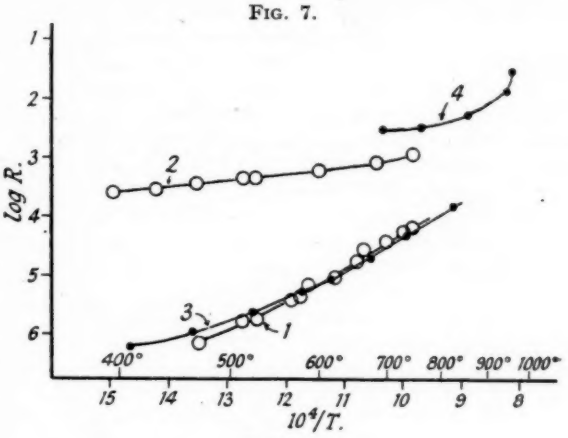
Cr_2O_3.

Chromic oxide, as prepared and ignited in air, evidently owes its conductivity to a small stoicheiometric excess of oxygen, and the states giving rise to the conductivity curves 2, 4, and 5 represent oxide approximating increasingly closely to the ideal composition Cr_2O_3. Nevertheless, the rapid response of the conductivity to changes in the oxygen pressure, and the fact that the conductivity is the same in air and in oxygen at 70 cm. pressure, preclude the view that any extensive reaction is involved in the change from the badly conducting " reduced " oxide to the better conducting oxide formed in air. Harbard and King (*J.*, 1938, 955; see also Cameron, Harbard, and King, *J.*, 1939, 55, for a bibliography of reported non-stoicheiometric oxides of chromium) stated that chromic oxide formed by the thermal decomposition of ammonium dichromate had the approximate composition $Cr_2O_{3\cdot13}$. It would appear from their paper that this was slowly converted into Cr_2O_3 on prolonged ignition in air, and was rapidly reduced in hydrogen, these changes being irreversible (since the ignition of Hg_2CrO_4 in air furnishes stoicheiometric Cr_2O_3). The processes involved in the change from curve 1 (Fig. 6) to curves 2, 4, or 5 were, however, reversible. We conclude that the oxide obtained by Harbard and King was metastable, and was not indicative of the stable range of existence of the Cr_2O_3 phase. Our results suggest that the range of composition of this phase is, in fact, only narrow. A minute stoicheiometric excess of oxygen would suffice to account for the observed conductivity.

Zinc Ferrite.—Neither cation in this structure is normally capable of any increase in valency, so that $ZnFe_2O_4$ should be an electron (metal excess) conductor. This is confirmed by the results plotted in Fig. 7. Curve 1 [combining three sets of measurements; $E = 1{\cdot}22$ e.v., $\kappa(600°) = 8{\cdot}3 \times 10^{-5}$] represents the conductivity in air, curve 2 [$E = 0{\cdot}25$ e.v., $\kappa(600°) = 7{\cdot}9 \times 10^{-5}$] that in vacuum. At the highest temperature of curve 2 (734°) the conductivity showed no drift on prolonged heating in vacuum. The change from curve 1 to curve 2 was reversible. A second plate (conductivity in air, curve 3), when heated to 960° in vacuum, showed a pronounced drift in conductivity which was not perfectly reversible on

cooling, nor was the original low conductivity restored on admission of air; at 710° a slow reaction with oxygen was apparent, in addition to the initial rapid change. The increase of conductivity clearly indicates some chemical dissociation, bringing about a permanent change of composition. Schröder (*Z. Elektrochem.*, 1940, **46**, 680; 1941, **47**, 196) found that $CdFe_2O_4$ underwent decomposition, attended with a loss of cadmium, above 900°, although Schröder and Schmäh (*ibid.*, 1942, **48**, 241, 301) and Schröder, Lähr, and Müller (*ibid.*, 1943, **49**, 38) found no evidence of any similar reaction with $ZnFe_2O_4$. However, under the conditions of our conductivity measurements, a specimen of zinc ferrite weighing 2·51 g. underwent a loss of weight of 0·06 g. in 4 hours at 1000° and a dynamic vacuum (p_{O_2} about 10^{-4} mm.). The product was black and had a high conductivity. The composition (as determined by direct analysis) changed from $Fe_2O_3 : ZnO = 1{\cdot}055$ initially to $Fe_2O_3 : ZnO = 1{\cdot}143$ ultimately, indicating that zinc (or zinc oxide) and oxygen had been lost simultaneously, according to the equation

FIG. 7.

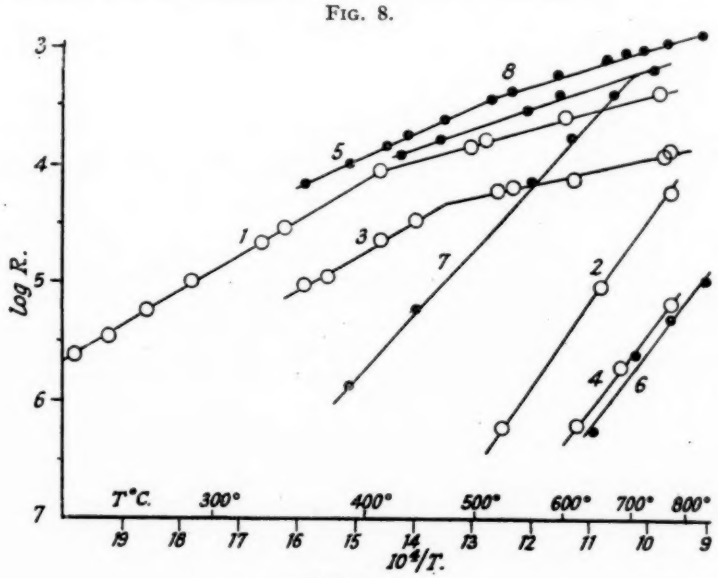


$ZnFe_2O_4$.

$$ZnFe_2O_4 \longrightarrow \underbrace{(1-x)ZnFe_2O_4 + \tfrac{2}{3}xFeFe_2O_4}_{\text{Mixed crystals.}} + xZnO + \tfrac{1}{6}xO_2$$

According to this equation, the composition corresponding to the observed loss in weight would be $Fe_2O_3 : ZnO = 1{\cdot}135$, in fair agreement with the observed change.

FIG. 8.



$ZnCr_2O_4$—I.

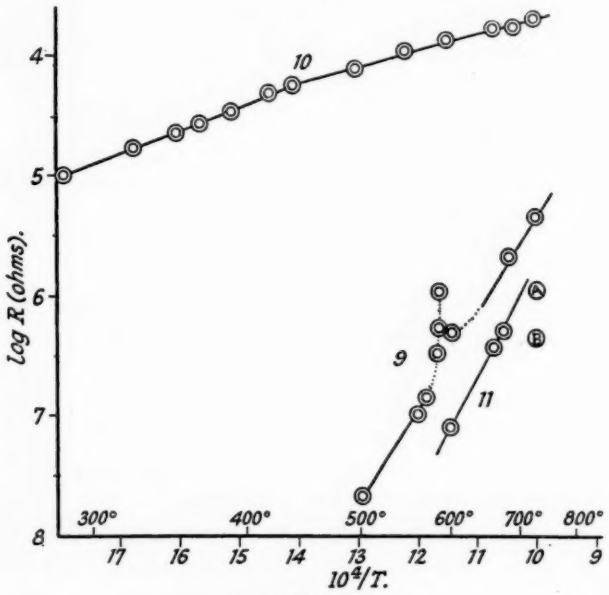
Zinc Chromite.—Some interest attaches to the properties of $ZnCr_2O_4$ since its surface properties and catalytic properties have been extensively studied, and also because the phenomena associated with the union of ZnO and Cr_2O_3 have been repeatedly investigated under varied experimental conditions. Data for two plates, sintered in air, are summarised in Fig. 8. Loss of oxygen, with formation of a stoicheiometric excess of interstitial zinc, or the

building on of excess oxygen atoms, with corresponding increase in the valency of Cr^{3+} cations, would *a priori* both be possible. The results show that zinc chromite is solely a positive hole conductor, due to the latter mechanism, and they suggest that a small stoicheiometric excess of oxygen must already be present in $ZnCr_2O_4$ formed by reaction in air.

The initial conductivity, in air, of plate 1 [curve 1, $E = 0{\cdot}59$ e.v., below 420°; $E = 0{\cdot}29$ e.v., $\kappa(600°) = 6{\cdot}5 \times 10^{-3}$ at higher temperatures] was substantially decreased in vacuum [curve 2, $E = 1{\cdot}47$ e.v., $\kappa(600°) = 6{\cdot}3 \times 10^{-5}$]. Admission of air at 530° restored the high conductivity (curve 3). Although the original conductivity of curve 1 was not completely regained, even after prolonged heating in air at 800°, the oxidised state represented by curve 3 was completely reproducible. In hydrogen [10 mm. pressure, admitted at 750°; curve 4, $E = 1{\cdot}23$ e.v., $\kappa(600°) = 1{\cdot}3 \times 10^{-5}$] the conductivity was reduced below the value obtained in vacuum. Readmission of oxygen at 620° restored the conductivity to that of curve 3.

A second plate (conductivity in air, curve 5) was heated in hydrogen (100 mm.) at 835°. The immediate initial increase in resistance of the plate was followed by a further effect,

FIG. 9.



$ZnCr_2O_4$—II.

increasing progressively with time; after 14 hours the conductivity–temperature curve was as shown in curve 6 [$E = 1{\cdot}37$ e.v., $\kappa(600°) = 6{\cdot}8 \times 10^{-6}$]. When air was readmitted at the ordinary temperature, a partial restoration of conductivity was observed [curve 7, $E = 1{\cdot}08$ e.v., $\kappa(600°) = 3{\cdot}5 \times 10^{-3}$]; after heating in air at 800°, the original conductivity of the air-sintered spinel was essentially restored (curve 8).

The hypothesis that a certain concentration of positive holes, *i.e.*, a small stoicheiometric excess of oxygen, is built into the crystal lattice of air-sintered $ZnCr_2O_4$ would account for the prolonged, slow interaction with hydrogen at 830° (a temperature probably about 100° above the Tammann point), and would enable the relation between curves 7 and 8, as also perhaps the discontinuities of slope of curves 1, 3, and 5, to be interpreted in terms of the interplay of surface and bulk-phase reactions, as discussed below. It would, then, be expected that zinc oxide and chromic oxide should react, in the absence of oxygen, to form a spinel of lower conductivity. This is, indeed, the case. Material sintered in hydrogen at 1050° had an extremely low initial conductivity; after exposure to the air at the ordinary temperature, the conductivity on heating in a vacuum (p_{O_2} about 10^{-4} mm.) followed curve 9 (Fig. 9) [$E = 1{\cdot}61$ e.v., $\kappa(600°) = 1{\cdot}05 \times 10^{-5}$]. Under these conditions the conductivity was comparable with that of the previous plate in hydrogen, but the higher value of E is indicative of a smaller concentration of built-in positive holes; the effect of exposure to the small partial pressure of

oxygen in the evacuated apparatus would be to displace the conductivity curve, as indicated by the—much larger—displacement of curve 7 relative to curve 6 (Fig. 8). An accidental small leakage of air at 510° produced a 10-fold increase of conductivity; admission of hydrogen (50 mm. pressure) reduced the zinc chromite to its original state. Air at 730° immediately raised the conductivity to a value somewhat less than that of air-sintered spinel [curve 10, $E = 0{\cdot}39$ e.v., below 440°; $E = 0{\cdot}26$ e.v., $\kappa(600°) = 3{\cdot}4 \times 10^{-3}$ at higher temperatures]. Finally, prolonged treatment with hydrogen or with carbon monoxide [curve 11, $E = 1{\cdot}83$ e.v., $\kappa(600°) = 2{\cdot}6 \times 10^{-6}$] lowered the conductivity still further, to an extent dependent on the partial pressure of reducing gas. Thus, the points *A* and *B* (Fig. 9) represent the resistance at 730° in 220 mm. pressure of hydrogen (after 16 hours) and in 410 mm. pressure of hydrogen (after 10 hours), respectively. These may be compared with the corresponding point on curve 9, in hydrogen at 50 mm. pressure.

These results can be correlated with experimental data on the formation of zinc chromite from the constituent oxides. The extensive work of Hüttig and of W. Jander, in particular, has shown that in the course of spinel formation and in similar reactions between solids, the changes brought about successively in a variety of physical and chemical properties provide an indication of the onset of surface mobility and of bulk diffusion respectively. The temperatures corresponding to the successive stages of the reaction process are, in general, related to the absolute melting point (T_m) of the compounds concerned, and can in fact be represented fairly well in terms of a common reduced temperature scale, expressed as T/T_m. In the formation of spinels, the mobility of the tervalent cations appears to be the factor chiefly determining the temperature of successive stages. Hence, the formation of ferrite spinels (m. p. of $Fe_2O_3 = 1570°$) should proceed throughout at lower temperatures than the formation of chromite spinels (m. p. of $Cr_2O_3 = 1990°$). Hüttig, Radler, and Kittel (*Z. Elektrochem.*, 1932, **38**, 442; Hüttig, *ibid.*, 1935, **41**, 527) found, however, that whereas the temperatures indicative of surface mobility, incipient inner diffusion, and spinel crystallisation in the system $ZnO + Fe_2O_3$ were 400—450°, less than 625°, and 675° respectively, the corresponding temperatures for $ZnO + Cr_2O_3$, heated in air, were 300°, 330—350°, and 400—500°. Jander and Weitendorf (*ibid.*, p. 435) showed that chromate could be leached out of the surface of such mixtures after they had been heated in air at temperatures as low as 400°, and also out of Cr_2O_3 itself after ignition in the presence of oxygen. They considered that the reaction $2ZnO + Cr_2O_3 + \frac{3}{2}O_2 \longrightarrow 2ZnCrO_4$ proceeded faster than the direct union to form $ZnCr_2O_4$. In hydrogen or in vacuum they found that the maximum surface activity was attained after heating at 500—550°, *i.e.*, at temperatures higher than obtain in the $ZnO + Fe_2O_3$ system.

An alternative interpretation of these results, which emerges from our work, is that chromic oxide and zinc chromite in air pick up a stoicheiometric excess of oxygen, which confers on them the observed electrical conductivity, but does not necessarily lead to the formation of $ZnCrO_4$ or—less likely still—CrO_3 as separate phases. The oxidising properties, or the extraction of chromate ion on leaching, could result from a disproportionation process, akin to the selective extraction of Mn^{2+} or Pb^{2+} when the higher oxides of manganese or lead are leached with nitric acid. It has been shown (Wagner, *Z. physikal. Chem.*, 1931, Bodenstein Festschr., 177; Anderson and Richards, *J.*, 1946, 537) that small departures from ideal stoicheiometric composition can result in a marked increase in rates of diffusion in solids, so that the greater reactivity of chromic oxide in the presence of oxygen might be interpreted as due to this factor. The influence of the gaseous atmosphere upon the conductivity and on the reactivity of the oxides would then both arise from the same primary process of interaction between the solid oxides and the gaseous phase.

It may be noted that the conductivity curve for zinc chromite given by Verwey, Haayman, and Romeijn (*J. Chem. Physics* 1947, **15**, 181) accords in slope with our air-sintered material. Evidently through fritting their $Fe_3O_4 + ZnCr_2O_4$ solid solutions in an atmosphere containing sufficient oxygen to inhibit the decomposition of the magnetite, they incorporated positive holes in their mixed crystals rich in zinc chromite. Their measurements on $Fe_3O_4 + ZnCr_2O_4$ and $Fe_3O_4 + MgCr_2O_4$ systems must, accordingly, refer to material capable of conduction both by free electrons and by positive holes. The operation of this second mechanism, with a higher activation energy, probably accounts for the form of their conductivity curves for solid solutions containing 50% and 60% of zinc chromite.

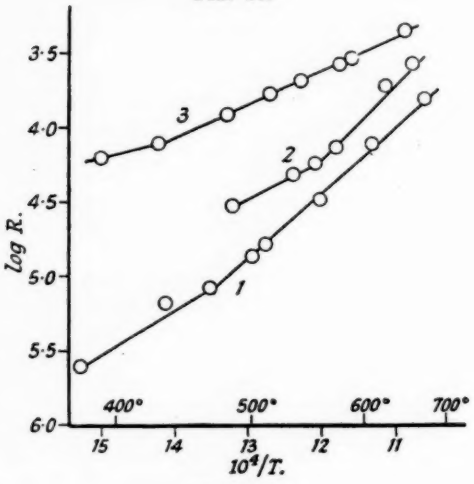
Magnesium Ferrite.—Measurements on the magnesium spinels were made at an early stage in the work, and were not extended over such a wide range of conditions as those on zinc spinels. The magnesium compounds resembled the latter in behaviour. Magnesium ferrite is an electron (metal excess) conductor. Curve 1 (Fig. 10, $E = 0{\cdot}92$ e.v.) represents the conductivity in air

(1 atm.), curve 3 ($E = 0{\cdot}46$ e.v.) that in vacuum, and curve 2 that in 4 mm. pressure of oxygen. Changes of conductivity with oxygen pressure were quite reversible.

Magnesium Chromite.—This is, as expected, a positive hole conductor. Measurements for an air-sintered specimen are shown in Fig. 11, on which is indicated also (dotted) the conductivity curve found by Jander and Stamm (*loc. cit.*), whose experimental method would inevitably include high contact resistances in the measured values, leading to a displacement of their curve relative to ours; the slope of their curve agrees with that found by us. Curve 1 (Fig. 11) represents the conductivity in air ($E = 0{\cdot}75$ e.v.), and curve 2 conductivity in 0·1 mm. pressure of air, after evacuation at 650° ($E = 0{\cdot}85$ e.v.).

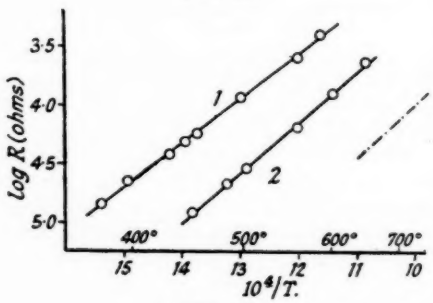
The results just summarised can be related to the recent discussion by Verwey and Heilmann (*J. Chem. Physics*, 1947, **15**, 174) and Verwey, Haaymann, and Romeijn (*loc. cit.*) of the relation between the particular structure of magnetite and its conducting properties. This compound, as they have shown, is an " inversed " spinel, $Fe^{3+}(Fe^{2+}Fe^{3+})O_4$, and they attribute its very high electronic conductivity to the facility with which an electron can pass, by a series of switches, along those lattice rows containing both Fe^{3+} and Fe^{2+} cations in the crystallographically equivalent positions of 6-fold co-ordination (Verwey and de Boer, *Rec. Trav. chim.*, 1936, **55**,

FIG. 10.



$MgFe_2O_4$.

FIG. 11.



$MgCr_2O_4$.

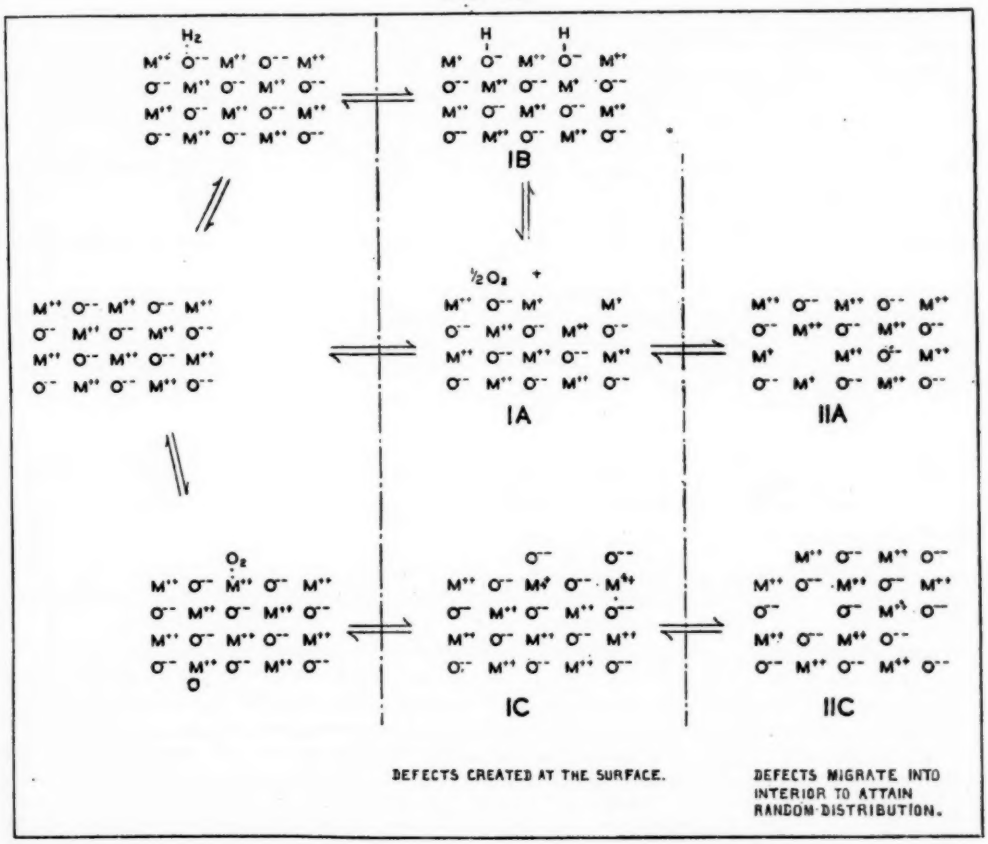
531). Zinc ferrite and zinc chromite are " normal " spinels, with the octahedrally co-ordinated cation positions occupied exclusively by the tervalent cations. The stoicheiometric compounds have, as our results indicate, at most a very low conductivity. When, by incorporation of a small stoicheiometric excess of oxygen, zinc chromite becomes a positive hole impurity conductor, the raising of some Cr^{3+} cations to a higher valency state realises the condition envisaged by Verwey, with chromium ions of mixed valencies in crystallographically equivalent positions, capable of propagating an electron switch along the [110] lattice rows. In zinc ferrite we may, by analogy, reasonably postulate that the excess electrons, remaining from the loss of a small proportion of oxygen from the crystal lattice, are accommodated by transformation of Fe^{3+} cations to Fe^{2+} cations, again providing the possibility of electron transference by Verwey's mechanism.

Conductivity due to the presence of interconvertible cations of mixed valency in the crystallographically equivalent tetrahedral positions is apparently less readily exhibited; possibly the longer spacing between such positions makes the requisite electronic transitions less probable. Thus, zinc chromite shows no sign of excess electron conduction, even in hydrogen at 800° (compare zinc oxide). It may be significant in this connection that we have also found $NiAl_2O_4$ to be a very poor conductor. This is a " normal " spinel (Verwey and Heilmann, *loc. cit.*), with all the Ni^{2+} cations in the tetrahedral positions. By analogy with the oxide, which was shown by Klemm and Hass (*Z. anorg. Chem.*, 1934, **219**, 82) to be non-stoicheiometric, NiO_{1+x}, it might be expected that this nickel spinel would show a marked tendency for positive hole conduction, through the elevation of some of the nickel cations to a

higher valency state. However, $NiAl_2O_4$ after being sintered in air at 1000° has a low conductivity at temperatures up to 735°, at least; the conductivity is rather worse in a vacuum than in air.

The observations summarised above have some bearing on a fundamental problem raised by Meyer and Möglich (*Z. Elektrochem.*, **1939**, **45**, 68) and Schottky (*ibid.*, p. 69): that of the temperature range over which the concept of a solid in statistical thermodynamic equilibrium, both internally and with its environment, is of valid application. Attainment of such equilibrium necessarily involves two distinct stages, involving the surface and the interior of the crystal lattice, respectively. These two stages together constitute the fundamental processes in chemical interactions between a gas and a solid phase.

FIG. 12.



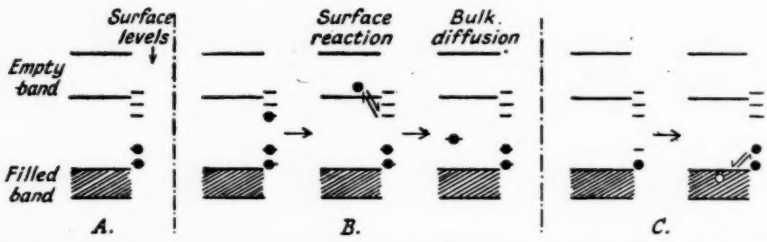
(I) The primary process of interaction involves the surface layers of atoms only, whereby in oxidation and reduction processes lattice defects (in the form of ions of " abnormal " charge) are formed. With oxides behaving as reduction semiconductors (ZnO, $ZnFe_2O_4$, etc.), as is diagrammatically represented in Fig. 12, oxygen may be evaporated directly from the surface of the crystal (I, A) or O^{2-} ions may be converted to OH^- ions through the chemisorption of hydrogen (I, B). In the latter case, subsequent loss of a molecule of water between two adjacent OH^- ions leads to the same ultimate state with one anion site vacant and two additional electrons accommodated on adjacent cations. With oxidation semiconductors (Cr_2O_3, $ZnCr_2O_4$) new anion sites are filled through the chemisorption of oxygen (I, C). The essential feature is that none of these processes depends on the mobility and redistribution of ions or atoms *within* the crystal lattice.

(II) In a state of thermodynamic equilibrium, there will (to a first approximation) be a random distribution of lattice defects throughout the crystal lattice, with a somewhat different distribution in the surface layers of atoms. The lattice defects, created at the surface as in (I)

must therefore diffuse into the interior of the crystal as in (II, A, II, C) in order that equilibrium may be attained. This step involves place-exchange of either anions or cations, and so can hardly be achieved below the Tammann temperature in the case of nearly stoicheiometric solids, although where marked deviations from stoicheiometric composition occur, self-diffusion may be important at lower temperatures. Hence, as pointed out by Meyer and Möglich, arguments based on attainment of thermodynamic equilibrium are valid only for investigations of semiconductors at sufficiently high temperatures. Meyer and Möglich accordingly distinguished between this high-temperature range ($T > 0{\cdot}5T_m$) and those lower temperatures which are necessarily characterised by frozen or false equilibria.

Our results show clearly that the processes of interaction of oxides with oxygen or hydrogen, leading to large changes in conductivity, occur freely and reversibly at temperatures so low that processes involving lattice diffusion can be excluded from consideration—*e.g.*, the increase in conductivity of zinc oxide in a vacuum at 500°, and the oxidation of zinc chromite at 530°. Further, when the potential leads from a zinc chromite plate were connected to an oscillograph, the changes in conductivity at 760° on alternate evacuation or admission of oxygen or hydrogen were seen to be sensibly instantaneous. The distinction between the immediate change in conductivity and the slower prolonged drift which ensued in hydrogen or carbon monoxide was very clear. Clearly (*a*) an excess or deficit of electrons resulting from changes in the population of the *surface layers* of atoms is sufficient to account for changes in conductivity of the magnitude found, without necessarily involving any change in bulk composition, and (*b*) such changes proceed rapidly and reversibly at temperatures convenient for the study of semiconducting properties. This last point has, unfortunately, been neglected by several recent workers—*e.g.*,

FIG. 13.



in the work of Miller (*loc. cit.*) on zinc oxide, and of Feldman (*Physical Rev.*, **1943**, **64**, 113) on cuprous oxide—who have attempted to " freeze " the concentration of stoicheiometric lattice defects.

Theoretical discussions of impurity semiconductors have been based on the idealised model of impurity levels in an infinite crystal lattice. Möglich and Rompe (*Physikal. Z.*, **1943**, **44**, 77), in a paper on the rôle of the surface in the reactivity of solids, have suggested a model that can be extended to interpret the observed relations between surface reactions of the type considered above, and the conductivity of solids. They point out that the permitted energies of electrons at the surface of a crystal are not identical with those of the three-dimensionally periodic lattice as a whole, so that for a finite, stoicheiometric crystal the energy scheme must include filled and unfilled surface levels, in addition to the energy bands of the crystal lattice (Fig. 13, *A*). Excitation of electrons in the surface levels (*e.g.*, photochemically) will be reflected in a change in the Boltzmann distribution of electrons between the filled band, the conduction band, and filled or vacant impurity levels of the crystal lattice. Conversely, the population and energy distribution of electrons in the surface levels—and hence the reactivity and properties of the surface (cf. Garner, *Chem. and Ind.*, **1947**, 132)—are profoundly modified by changes in the concentration of impurity levels within the crystal. When oxygen is evaporated out of, or built on to, the surface of an originally stoicheiometric oxide, the net effect is that electrons are added to (Fig. 13, *B*) or removed from (Fig. 13, *C*) the surface levels. Excitation of electrons to the conduction band, or out of the filled valency band, then follows in consequence of the thermal energy of the crystal. If the temperature permits of the necessary ionic mobility, the formation of new impurity centres *within* the crystal, to which a transference of electrons from surface levels takes place, will then ensue. There is thus no paradox involved in the observation that the semiconducting properties may change reversibly and reproducibly as a result of processes which affect only the surface, without attainment of true equilibrium.

There is, as has been stated above, a lower limit of temperature below which equilibration of

the surface with the gas phase does not occur with sensible speed. At lower temperatures conducting properties are not reproducible, being entirely dependent on the previous thermal history of each specimen, and showing a drift towards equilibrium values with the onset of surface mobility. Our observations indicate that the condition of reproducibility is achieved above about $0{\cdot}25$—$0{\cdot}3T_m$. Many studies of semiconductors—including nearly all measurements of Hall effect and electronic mean free paths—have been made at temperatures below $0{\cdot}3T_m$; the theoretical significance of such work is very doubtful.

We accordingly recognise three ranges of temperature which determine the properties and reactivity of solid oxides and similar compounds.

(i) Temperatures above about $0{\cdot}5T_m$, at which attainment of true equilibrium is possible. Lattice defects created at the surface can migrate into the crystal lattice, so that a heterogeneous reaction can proceed to completion.

(ii) An intermediate temperature range, roughly $0{\cdot}3T_m$ to $0{\cdot}5T_m$, at which the surface, but not the bulk phase, can interact reversibly with the gaseous atmosphere. Only if the solid has a stoicheiometric range wide enough to produce large changes in the magnitude of the diffusion coefficient can reaction in the ordinary sense proceed. In general, reaction with a gas or with other solids (*e.g.*, spinel formation) can give rise only to surface compounds.

(iii) A low temperature range, below $0{\cdot}3T_m$, in which surface equilibrium is also frozen.

These views accord entirely with those of Garner (*loc. cit.*), based on a different experimental approach. The reversible pick-up of oxygen from, or loss of oxygen to, the gas phase can be regarded as a process of chemisorption or desorption, the rate of which is dependent on the temperature and the activation energy of the sorption process. Attainment of adsorptive equilibrium implies a degree of mobility of the surface atom layers, and it is therefore not fortuitous that the temperature above which the semiconducting properties display reversibility should be close to that at which, in Hüttig's studies of the phenomenology of fritting processes and solid reactions, the change in properties of solids gives evidence of surface diffusion processes.

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352. *The Preparation of Some Branched-chain Monocarboxylic Acids.*

By A. D. CAMPBELL, C. L. CARTER, and S. N. SLATER.

A method is described for preparing monocarboxylic acids containing a quaternary carbon atom in the γ-position to the carboxyl group by condensation of vinyl cyanide with ketones of appropriate structure and the subsequent hydrolysis and reduction (mainly by the Wolff–Kishner method) of the resulting keto-cyanides.

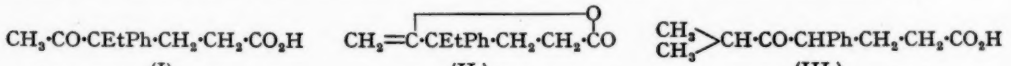
THE natural occurrence of a number of branched-chain monocarboxylic acids of physiological importance has stimulated interest in their pure chemistry. The most difficultly accessible of these acids are those containing a quaternary carbon atom, and until recently there were few general methods available for their preparation. The present communication describes a general method for the preparation of monocarboxylic acids containing a quaternary carbon atom in the γ-position to the carboxyl group, based upon the elegant cyanoethylation procedure developed more particularly by Bruson and his co-workers (*J. Amer. Chem. Soc.*, 1942, **64**, 2457 and later papers, especially *ibid.*, p. 2850). These authors have shown that vinyl cyanide condenses smoothly in the presence of alkali with compounds containing active hydrogen (*e.g.*, a methylene group activated by an adjacent carbonyl group) to give (in the example quoted) keto-cyanides which can be hydrolysed to 4-keto-carboxylic acids. When either a methyl or a methylene group is available, the methylene group as expected proves the more reactive. As is shown below, a $CH\lessgtr$ group is also selectively activated. These keto-acids can be reduced to yield acids of the required type, the general course of the synthesis thus being :

$$R{\cdot}CO{\cdot}CHR'R'' + CH_2{:}CH{\cdot}CN \longrightarrow R{\cdot}CO{\cdot}CR'R''{\cdot}CH_2{\cdot}CH_2{\cdot}CN \xrightarrow{\text{(2 stages)}} R{\cdot}CH_2{\cdot}CR'R''{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$$

To test the generality of the method, several of the readily accessible aryl alkyl ketones were first examined. *iso*Butyrophenone reacted smoothly with vinyl cyanide to give 3-*benzoyl*-iso*amyl cyanide* which was hydrolysed with aqueous potassium hydroxide to 3-*benzoyl*-3-*methyl*-*butanecarboxylic acid*. This was reduced in good yield by the Clemmensen process to 4-*phenyl*-3 : 3-*dimethylbutanecarboxylic acid*. Propiophenone was alkylated with sodamide and butyl iodide to give ω-*methyl*-ω-n-*butylacetophenone* which with vinyl cyanide gave 3-benzoyl-3-

methylheptyl cyanide, and this was hydrolysed to the *acid*. This could not be reduced completely by the Clemmensen process, but reduction by the modified Wolff–Kishner method (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487) yielded **3-*benzyl*-3-*methylheptanecarboxylic acid***. Starting with **ω-*methyl*-ω-n-*octylacetophenone*** (from propiophenone, sodamide, and *n*-octyl iodide), **3-*benzoyl*-3-*methylundecanecarboxylic acid*** was prepared and reduced to **3-*benzyl*-3-*methylundecanecarboxylic acid***. In an attempted preparation of 3-benzyl-3-ethylhexanecarboxylic acid, however, although the intermediate **3-*benzoyl*-3-*ethylhexanecarboxylic acid*** was prepared by the cyanoethylation procedure from **ω-*ethyl*-ω-*propylacetophenone*** it was only partially reduced by the Wolff–Kishner method. In these examples the structures of the cyanides and keto-acids must be those assumed, since only one active position is open to attack in the ketone.

The next two examples of these acids were prepared from benzyl methyl ketone by monoalkylation followed by reaction with vinyl cyanide, hydrolysis, and reduction. Here it has been assumed that the point of attack must be at the doubly activated position between the benzene ring and the carbonyl group. Ethylation of benzyl methyl ketone followed by cyanoethylation and hydrolysis gave **3-*acetyl*-3-*phenylpentanecarboxylic acid*** (I). As expected, this proved resistant to Clemmensen reduction, and an attempted reduction with red phosphorus and hydriodic acid gave a crystalline *product*, $C_{14}H_{16}O_2$, whose structure is not apparent from its general behaviour. It liberates carbon dioxide from aqueous sodium carbonate and is unsaturated, perbenzoic-acid titration indicating the presence of one double bond. The molecular formula and unsaturation could be accommodated in a lactone structure (II),*



(I). (II.) (III.)

and it is known that γ-keto-acids may be transformed into unsaturated lactones under the influence of such reagents as acetic anhydride, but the reaction of the above product with carbonate solution was more characteristically that of an acid than a lactone. In an attempt to prepare such a lactone, 3-acetyl-3-phenylpentanecarboxylic acid was refluxed with acetic anhydride, but no homogeneous material of the desired composition was obtained from the neutral fraction of the distilled product. For further comparison a specimen of **3-*phenyl*-3-*isobutyrylpropanecarboxylic acid*** (III), in which the carbonyl group is flanked on each side by CH groups, was prepared by cyanoethylation of benzyl *iso*propyl ketone and hydrolysis. This acid was recovered largely unchanged after being heated with syrupy phosphoric acid containing phosphoric oxide, and after being heated with acetic anhydride. Reduction of the acetylphenylpentanecarboxylic acid by the Wolff–Kishner method gave the required **3-*phenyl*-3-*ethylpentanecarboxylic acid***. Octylation of benzyl methyl ketone gave **3-*phenylundecan*-2-*one***, and this on cyanoethylation and hydrolysis yielded **3-*acetyl*-3-*phenylundecanecarboxylic acid***, reduced by the Wolff–Kishner process to **3-*phenyl*-3-*ethylundecanecarboxylic acid***.

Finally, some specimens of purely aliphatic acids of the type under consideration were prepared. 3-Acetyl-3-methylbutanecarboxylic acid was prepared from methyl *iso*propyl ketone, its melting point and that of its semicarbazone agreeing satisfactorily with the recorded figures and confirming the view that the $CH\lessgtr$ group rather than the methyl group would be attacked by the vinyl cyanide. It was partially reduced by prolonged Clemmensen treatment, and by careful fractionation of the product a specimen of pure **3 : 3-*dimethylpentanecarboxylic acid*** was obtained. **3 : 3-*Dimethylnonane*-** and **3 : 3-*dimethyltridecane*-*carboxylic acid*** were obtained in the same way from the appropriate ketones, the final reduction being achieved by the Wolff–Kishner method.

The characterisation of these acids proved difficult, and the only satisfactory crystalline derivatives prepared were the *S*-benzylthiouronium salts (Donleavy, *J. Amer. Chem. Soc.*, 1936, **58**, 1004). The acids themselves were mostly viscous liquids showing little tendency to crystallise, although some crystallised on long standing.

In the preparation of 3-benzoyl-3-methylbutanecarboxylic acid an attempt was made to hasten the slow hydrolysis of the cyanide by addition of methyl alcohol to the reaction mixture.

* The authors are indebted to Dr. A. J. Birch for the suggestion that the substance is probably a dihydroresorcinol derivative :

Dr. Birch has observed the formation of such a substance from a similar keto-acid by the action of sulphuric acid.

Rapid reaction occurred, but the product, a crystalline substance melting at 102—103°, was obviously not the expected acid. It proved to be the *lactone* of 4-*hydroxy*-4-*phenyl*-3 : 3-*dimethylbutanecarboxylic acid* (IV), resulting evidently from the reduction of the carbonyl group of the primary product of hydrolysis, the keto-acid, by the aqueous methyl-alcoholic potash.

(IV.) $C_6H_5\cdot CH(O\cdot CO)\cdot CMe_2\cdot CH_2\cdot CH_2$

The use of methyl alcohol as a reducing agent is familiar in some fields, but the reduction of ketones by this method may not be so well known, although the use of metal alkoxides and alcohols is now common. An early example of this type of reaction is the conversion of camphor into borneol by means of alcoholic potash (Berthelot, *Ann. Chim.*, **1859**, **56**, 51), and the reduction of benzophenone to benzhydrol by alcoholic potash has been reported by several workers (*e.g.*, Saqumenny, *Annalen*, **1877**, **184**, 174; Montagne, *Rec. Trav. chim.*, **1908**, **27**, 334). The latter reduction proceeds well in the presence of a large excess of 30% methyl-alcoholic potassium hydroxide, but with only one molecular proportion of potassium hydroxide no reduction was observed. When *iso*propyl alcohol was used the reaction proceeded well in the presence of a moderate excess of potassium hydroxide.

Experimental.

3-*Benzoyl*isoa*myl Cyanide.*—Vinyl cyanide (21·2 g.) was added dropwise with stirring to a solution of *iso*butyrophenone (60 g.) in dioxan (100 g.) containing 5 c.c. of 30% methyl-alcoholic potassium hydroxide. The product was poured into water and the oil separated, dried, and distilled. After low-boiling material (including 20 g. of recovered and redistilled *iso*butyrophenone, b. p. 108°/23 mm.) had been removed, the required *cyanide* was obtained as a viscous oil (31 g.), b. p. 194—200°/23 mm. (Found : N, 7·4. $C_{13}H_{15}ON$ requires N, 7·0%).

3-*Benzoyl*-3-*methylbutanecarboxylic Acid.*—The cyanide (25·5 g.) was refluxed and stirred vigorously with a solution of potassium hydroxide (25 g.) in water (120 c.c.) until evolution of ammonia ceased. The reaction mixture was acidified, extracted with chloroform, dried, and distilled, yielding the *acid* (23 g.) as a viscous oil distilling almost entirely at 213°/18 mm. (Found : C, 70·6; H, 7·13. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·28%). The acid was characterised as the *semicarbazone* which crystallised from alcohol in small clumps of needles, m. p. 202—203° (decomp.) (Found : N, 15·0. $C_{14}H_{19}O_3N_3$ requires N, 15·2%).

4-*Phenyl*-3 : 3-*dimethylbutanecarboxylic Acid.*—The above keto-acid (22 g.) in toluene was refluxed with amalgamated zinc (100 g.) and excess of somewhat diluted hydrochloric acid for 24 hours with addition from time to time of further quantities of concentrated hydrochloric acid. The *acid* (17·5 g.) was isolated as a viscous oil, the bulk distilling at 181°/15 mm. (Found : C, 75·7; H, 8·34. $C_{13}H_{18}O_2$ requires C, 75·8; H, 8·74%). The S-*benzylthiouronium* salt had m. p. (from alcohol) 148° (Found : N, 7·3. $C_{21}H_{28}O_2N_2S$ requires N, 7·5%).

ω-Methyl-ω-n-*butylacetophenone.*—Propiophenone (27 g.) in benzene was alkylated with sodamide (9 g.) and *n*-butyl iodide (37 g.), and worked up to give the *ketone* (20 g.) as a viscous oil, b. p. 133—138°/15 mm. (Found : C, 81·6; H, 9·91. $C_{12}H_{18}O$ requires C, 82·1; H, 9·47%). The orange-coloured 2 : 4-*dinitrophenylhydrazone* had m. p. 74·5—75° (Found : N, 15·3. $C_{19}H_{22}O_4N_4$ requires N, 15·1%).

3-*Benzoyl*-3-*methylheptanecarboxylic Acid.*—The above ketone (18 g.) in dioxan was treated dropwise with vinyl cyanide (6 g.) in the presence of a small quantity of methyl-alcoholic potash, and the mixture kept at 50—60° for a few hours. The product was worked up to give the cyanide (5 g.) as a clear liquid, b. p. 210—215°/15 mm. A repetition of this preparation, using *tert.*-butyl alcohol as solvent, resulted in a more vigorous reaction and a better yield (6 g. of cyanide from 10 g. of ketone). The cyanide (11 g.) was hydrolysed with excess of concentrated aqueous potassium hydroxide, evolution of ammonia taking place slowly during about 12 hours' refluxing. The *acid* was obtained as a thick viscous oil (7 g.), b. p. 238°/16 mm. (Found : C, 72·5; H, 8·92. $C_{16}H_{22}O_3$ requires C, 73·3; H, 8·4%).

3-*Benzyl*-3-*methylheptanecarboxylic Acid.*—The keto-acid was only partly reduced in toluene by the Clemmensen method during 20 hours (Found, on a specimen of the distillate of b. p. 216—218°/14 mm.: C, 74·7; H, 8·86. Calc. for $C_{16}H_{24}O_2$: C, 77·4; H, 9·68%). The keto-acid was therefore reduced by the modified Wolff–Kishner method; a mixture of the acid (3 g.), 50% hydrazine hydrate (3 c.c.), and sodium hydroxide (1 g.) in 2 : 2′-dihydroxydiethyl ether (10 c.c.) was refluxed for 1½ hours, and water then removed in a slow current of air until the temperature of the mixture rose to 195°; refluxing was then continued on the oil-bath for 4 hours. The product was worked up to give the *acid* (2 g.) as a viscous oil, b. p. 197—200°/11 mm. (Found : C, 77·7; H, 9·81%). The S-*benzylthiouronium* salt had m. p. (from alcohol) 122° (Found : N, 7·0. $C_{24}H_{32}O_2N_2S$ requires N, 6·8%).

ω-Methyl-ω-n-*octylacetophenone.*—Propiophenone (21 g.) in benzene was gently refluxed with sodamide (7 g.), and octyl iodide (36 g.) was then added with stirring. After an induction period a vigorous reaction took place. The mixture was refluxed for 1½ hours, left overnight, and worked up to give the *ketone* (20 g.) as a viscous oil, b. p. 183—187° (Found : C, 83·0; H, 10·57. $C_{17}H_{26}O$ requires C, 82·9; H, 10·57%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in yellow platelets, m. p. 88—89° (Found : N, 13·4. $C_{23}H_{30}O_4N_4$ requires N, 13·1%).

3-*Benzoyl*-3-*methylundecanecarboxylic Acid.*—The above ketone (19 g.) in dioxan was cyanoethylated with vinyl cyanide (5 g.) in the presence of methyl-alcoholic potash to give after distillation unchanged ketone (13 g.) and a rather poor yield (6 g.) of cyanide. By carrying out the reaction in *tert.*-butyl alcohol, however, an excellent yield was obtained (13 g. of cyanide, b. p. 190—197°/1 mm., from 13 g.

of ketone). The cyanide (12 g.) was hydrolysed (12 hours) by excess of aqueous potassium hydroxide to give the *acid*, which was obtained as a thick yellow oil (8 g.), b. p. 223—225°/1 mm. (Found: C, 75·0; H, 9·60. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·43%).

3-*Benzyl*-3-*methylundecanecarboxylic Acid*.—The keto-acid (8 g.), 50% hydrazine hydrate (10 c.c.), and sodium hydroxide (3 g.) in 2 : 2′-dihydroxydiethyl ether (40 c.c.) were refluxed for 1½ hours, and water was then removed until the temperature of the liquid reached 195°; refluxing was then continued for 4 hours. The *acid* was obtained as a white solid (4 g.), b. p. 207—208°/1 mm., which crystallised in fine needles, m. p. 81°, from methyl alcohol (Found: C, 79·2; H, 10·31. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·5%). The S-*benzylthiouronium* salt had m. p. (from alcohol) 145° (Found: N, 5·9. $C_{28}H_{42}O_2N_2S$ requires N, 6·2%).

3-*Benzoyl*-3-*ethylhexanecarboxylic Acid*.—ω-Ethyl-ω-*n*-propylacetophenone (38 g.) in dioxan was cyanoethylated to give a small high-boiling fraction together with a large amount of unchanged ketone (26 g.). The crude cyanide was slowly hydrolysed by aqueous potassium hydroxide to give the required *acid*, isolated as a thick viscous oil (4·5 g.), b. p. (redistilled) 220°/16 mm. (Found: C, 73·1; H, 8·26. $C_{16}H_{22}O_3$ requires C, 73·3. H, 8·4%). This acid underwent partial reduction under Wolff–Kishner conditions, giving a small amount (1·5 g.) of a yellow oil with a characteristic unpleasant odour of burned fat, b. p. *ca.* 175°/1 mm. (Found: C, 75·5; H, 8·99. Calc. for $C_{16}H_{24}O_2$: C, 77·4; H, 9·68%).

3-*Acetyl*-3-*phenylpentanecarboxylic Acid*.—Benzyl methyl ketone (27 g.) in benzene was alkylated with sodamide (8 g.) and ethyl iodide (33 g.) to give 3-phenylpentan-2-one as a clear mobile liquid (23 g.), b. p. 123—125°/24 mm. The semicarbazone crystallised in white platelets from aqueous acetone, m. p. 190—191° (Suter and Wilson, *J. Amer. Chem. Soc.*, 1942, **64**, 533, give m. p. 190·5—191·5°). The ketone (14 g.) in dioxan was cyanoethylated (6 g. of vinyl cyanide) to give the required cyanide as a slightly yellow viscous oil (11 g.), b. p. 205—215°/23 mm. The cyanide (27 g.) was hydrolysed to give the *acid* (27 g.), b. p. 193—197°/2—3 mm. By crystallisation from light petroleum (b. p. 60—80°) in the presence of a little chloroform it was obtained as clear diamond-shaped crystals, m. p. 78° (Found: C, 71·8; H, 7·6. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). It did not give a semicarbazone or a dinitrophenylhydrazone.

3-*Phenyl*-3-*ethylpentanecarboxylic Acid*.—(*a*) After an attempted reduction of the above keto-acid by the Clemmensen method for 20 hours, almost all the starting material was recovered unchanged.

(*b*) *Reduction with red phosphorus and hydriodic acid*. The keto-acid (7 g.) was refluxed with potassium iodide (2 g.) and red phosphorus (6 g.) in phosphoric acid (70 c.c.) and water (10 c.c.) for 6 hours. The mixture was poured into water, filtered, and ether-extracted. After being washed with sodium thiosulphate solution the ethereal solution was dried and distilled, giving a syrupy yellow oil (3 g., b. p. 195—200°/2—4 mm.) which set to a glassy mass. By being warmed with ether the material was obtained in the form of white crystals, m. p. 156° [Found: C, 77·8, 77·6; H, 7·64, 7·53; *M* (Rast), 218. $C_{14}H_{16}O_2$ requires C, 77·7; H, 7·41%; *M*, 216). The *substance* liberated carbon dioxide from aqueous sodium carbonate, decolourised alkaline permanganate immediately, and reacted readily with bromine in chloroform. Perbenzoic acid titration indicated the presence of one double bond (0·0076 g. of substance reacted with 0·00608 m.e. of perbenzoic acid. Calc.: 0·00703 m.e.). By refluxing with excess of acetic anhydride the substance was partly converted into neutral material, but no pure product was isolated.

(*c*) *Wolff–Kishner reduction*. The keto-acid (7 g.), 50% hydrazine hydrate (10 c.c.), and sodium hydroxide (3 g.), after working up, gave the *acid* (3 g.) as a clear syrupy liquid, b. p. 155—165°/1—2 mm., with a characteristic smell of burned fat (Found: C, 75·8; H, 8·9. $C_{14}H_{20}O_2$ requires C, 76·4; H, 9·1%). The S-*benzylthiouronium* salt had m. p. (from alcohol) 153—154° (Found: N, 7·4. $C_{22}H_{30}O_2N_2S$ requires N, 7·3%).

3-*Phenyl*-3-iso*butyrylpropyl Cyanide*.—Vinyl cyanide (10 g.) was added slowly with shaking to benzyl *iso*propyl ketone (27 g.) in dioxan containing a small quantity of 30% methyl-alcoholic potash. The mixture became hot; after 3 hours it was poured into water, acidified, and extracted with ether. Distillation gave the *cyanide* (27 g.) as a clear mobile liquid, b. p. 218—222°/71 mm. (Found: N, 6·4. $C_{14}H_{17}ON$ requires N, 6·5%).

3-*Phenyl*-3-iso*butyrylpropanecarboxylic Acid*.—The above cyanide (26 g.) was saponified with a concentrated aqueous solution of potassium hydroxide (20 g.) by refluxing overnight. The potassium salt, which had separated as an oily layer which congealed on cooling, was dissolved in water and the acid precipitated with hydrochloric acid. On standing, it slowly solidified. It was dissolved in chloroform, and the solution dried and distilled to give a very viscous oil (25 g., b. p. 235—237°/64 mm.) which slowly crystallised. Crystallisation from light petroleum (b. p. 80—100°) gave the *acid* as clusters of needles, m. p. 71·5° (after some previous softening) (Found: C, 71·7; H, 7·6. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). By heating the acid with excess of syrupy phosphoric acid containing phosphoric oxide, a dark wine-red solution was obtained; after pouring this into water and working up through the sodium salt (charcoal), a crude material was obtained which immediately decolourised alkaline permanganate, but the only pure compound isolated from it was the unchanged keto-acid. After being refluxed for several hours with excess of acetic anhydride the keto-acid was recovered largely unchanged, and more prolonged treatment gave only a small amount of neutral material from which no pure compound was isolated.

3-*Phenylundecan*-2-*one*.—Benzyl methyl ketone (32 g.) in benzene was alkylated with sodamide (10 g.) and octyl iodide (54 g.), and, after working up, the *ketone* was obtained as a clear liquid (27 g.), b. p. 173—174°/14 mm. (Found: C, 82·6; H, 10·78. $C_{17}H_{26}O$ requires C, 82·9; H, 10·57%). The *semicarbazone* separated from alcohol as a white powder, m. p. 57° (Found: N, 13·8. $C_{18}H_{29}ON_3$ requires N, 13·9%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in yellow needles, m. p. 51° (Found: N, 13·6. $C_{23}H_{30}O_4N_4$ requires N, 13·1%).

3-*Acetyl*-3-*phenylundecanecarboxylic Acid*.—The above ketone (26 g.) in *tert.*-butyl alcohol was cyanoethylated with vinyl cyanide (7 g.) in the presence of methyl-alcoholic potash to give the cyanide (14 g.) as a slightly yellow viscous oil, b. p. 217°/2—3 mm. Alkaline hydrolysis of the cyanide (12 g.) with vigorous stirring and refluxing for 16 hours followed by acidification, extraction with chloroform, drying, and distillation gave the required *acid* (7 g.) as a thick liquid (b. p. 230°/1 mm.) which solidified.

It was crystallised from light petroleum, from which it separated as a white powder, m. p. 63° (Found: C, 75·9; H, 9·72. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·43%).

3-*Phenyl*-3-*ethylundecanecarboxylic Acid*.—The above keto-acid (6 g.) was reduced with 50% hydrazine hydrate (8 c.c.), sodium hydroxide (3 g.), and 2 : 2′-dihydroxydiethyl ether to give the required *acid* (3 g.) as a yellow oil, b. p. 205—210°/1 mm., with a peculiar fatty odour (Found: C, 78·2; H, 10·10. $C_{20}H_{32}O_2$ requires C, 78·9; H, 10·52%). The *S*-benzylthiouronium salt could not be prepared in a crystalline form.

3 : 3-*Dimethylpentanecarboxylic Acid*.—Vinyl cyanide (30 g.) and methyl *iso*propyl ketone (42 g.) in *tert*.-butyl alcohol (6 g.) containing 10 c.c. of 30% methyl-alcoholic potash gave 3-acetyl*iso*amyl cyanide (41 g.), b. p. 134°/18 mm., which was hydrolysed with aqueous potassium hydroxide to the corresponding acid (42 g.), b. p. 173—175°/21 mm., which solidified to a brittle solid, m. p. 40—45°, raised by 3 crystallisations to 46·5—47° (Blaise, *Bull. Soc. chim.*, 1899, **21**, 719, gives m. p. 48—49°). The semicarbazone had m. p. 186° (decomp.) (Blaise, *loc. cit.*, gives m. p. 185°). The keto-acid (10 g.), potassium iodide (2 g.), red phosphorus (6 g.), phosphoric acid (70 c.c.), and water (10 c.c.) gave, after refluxing for 5 hours and working up, a product, b. p. 150—160°/21 mm., from which unchanged keto-acid crystallised on standing. The oily residue was redistilled to give a clear liquid whose analytical figures indicated only partial reduction (Found: C, 64·5; H, 8·69. $C_9H_{16}O_3$ requires C, 66·7; H, 11·11%). By prolonged Clemmensen reduction a small amount of pure 3 : 3-*dimethylpentanecarboxylic acid* was obtained; the keto-acid (10 g.) in toluene (20 c.c.) was refluxed for 40 hours with amalgamated zinc (20 g.), water (15 c.c.), concentrated hydrochloric acid (35 c.c.), and glacial acetic acid (2 c.c.), further addition of hydrochloric acid being made at the rate of 10 c.c. every 6 hours. The toluene layer was separated and added to an ethereal extract of the aqueous layer, dried, and distilled, giving two fractions: (*a*) b. p. 130—150°/16 mm. (4 g.), (*b*) b. p. 165—170°/16 mm. (6 g., unchanged keto-acid). Fraction (*a*) was redistilled, and a portion of the middle distillate analysed (Found: C, 66·7; H, 11·23%). The acid was characterised as the *S-benzylthiouronium* salt, m. p. (from alcohol) 150° (Found: N, 9·4. $C_{16}H_{26}O_2N_2S$ requires N, 9·0%).

3-*Hexoyl*-3-*methylbutanecarboxylic Acid*.—*iso*Propyl amyl ketone (16 g.) was cyanoethylated with vinyl cyanide (7 g.) in *tert*.-butyl alcohol in the presence of a small amount of methyl-alcoholic potash to give the cyanide as a yellow oil, b. p. 156—159°/11 mm. The cyanide (9 g.) was hydrolysed by 10 hours' refluxing with concentrated aqueous potassium hydroxide and worked up to yield the corresponding acid as a yellow oil (4 g.), b. p. 181—183°/10 mm., which was not yet pure, although giving a satisfactory product on reduction in the next stage (Found: C, 66·1, 65·9; H, 10·0, 10·1. Calc. for $C_{12}H_{22}O_3$: C, 67·3; H, 10·28%).

3 : 3-*Dimethylnonanecarboxylic Acid*.—The above keto-acid was reduced by the Wolff–Kishner method (3 c.c. of 50% hydrazine hydrate, 1 g. of sodium hydroxide, 20 c.c. of 2 : 2′-dihydroxydiethyl ether) to give the *acid* (2 g.) as a liquid with a peculiar fatty odour, b. p. 157°/10 mm. (Found: C, 71·6; H, 12·1. $C_{12}H_{24}O_2$ requires C, 72·0; H, 12·0%). The S-*benzylthiouronium* salt had m. p. (from alcohol) 133° (Found: N, 7·7. $C_{20}H_{34}O_2N_2S$ requires N, 7·8%).

2-*Methyldodecan*-3-*one*.—A mixture of nonanecarboxylic acid (0·5 mol.) and *iso*butyric acid (1 mol.) was passed over a thoria catalyst supported on pumice at a furnace temperature of 450—470°. The distillate was neutralised, dried, and distilled, giving the following fractions: (*a*) di*iso*propyl ketone (20 g.), (*b*) iso*propyl nonyl ketone*, b. p. 150—151°/16 mm., m. p. −1° (16 g.) (Found: C, 78·3; H, 13·12. $C_{13}H_{26}O$ requires C, 78·8; H, 13·13%). Crystalline derivatives were obtained with 2 : 4-dinitrophenylhydrazine (orange plates, m. p. 36°) and semicarbazide (m. p. 50—51°), but in spite of repeated recrystallisations satisfactory figures for the nitrogen content of these derivatives were not obtained, Kjeldahl determinations (which had given satisfactory results in all other cases in this series) being erratic and unreproducible.

3-*Decoyl*-3-*methylbutanecarboxylic Acid*.—The above ketone (15 g.) in *tert*.-butyl alcohol was cyanoethylated with vinyl cyanide (5 g.) in the presence of methyl-alcoholic potash, a vigorous reaction taking place. The cyanide was obtained as a yellow oil (12 g.), b. p. 210—220°/10 mm., which solidified on freezing; m. p. 10°. The cyanide was slowly hydrolysed by refluxing with excess of aqueous potassium hydroxide, and the product worked up to give the corresponding *acid* (7 g.), b. p. 225—230°/10 mm., which solidified on cooling. It was recrystallised from light petroleum; m. p. 43° (Found: C, 71·4; H, 11·48. $C_{16}H_{30}O_2$ requires C, 71·1; H, 11·16%).

3 : 3-*Dimethyltridecanecarboxylic Acid*.—The keto-acid (6 g.) was reduced by the Wolff–Kishner process (using 4 c.c. of 50% hydrazine hydrate, 3 g. of sodium hydroxide, and 30 c.c. of 2 : 2′-dihydroxydiethyl ether) to give the *acid* (3 g.), b. p. 200—205°/10 mm., as a fatty-smelling liquid (Found: C, 75·3; H, 12·5. $C_{16}H_{32}O_2$ requires C, 75·0; H, 12·5%). The S-*benzylthiouronium* salt had m. p. (from alcohol) 134° (Found: N, 6·6. $C_{24}H_{42}O_2N_2S$ requires N, 6·5%).

The Lactone of 4-*Hydroxy*-4-*phenyl*-3 : 3-*dimethylbutanecarboxylic Acid*.—3-Benzoyl*iso*amyl cyanide (28 g.) was treated with excess of a concentrated aqueous solution of potassium hydroxide (30 g.), and sufficient methyl alcohol added to make the mixture homogeneous. On refluxing, a rapid evolution of ammonia took place, and when this had ceased the product was diluted with water, acidified, and extracted with chloroform. The dried extract was distilled, yielding a viscous oil (20 g.), b. p. 117—125°/26 mm., which solidified slowly. The *lactone* crystallised from light petroleum (80—100°) as felted white needles, m. p. 102—103° (Found: C, 76·5; H, 7·9. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%). It was not affected by dilute aqueous sodium carbonate in the cold, but reacted on heating. The resulting solution was stable to permanganate.

Reduction of Benzophenone.—Benzophenone (5 g.) was refluxed overnight with a large excess of methyl-alcoholic potash, diluted with water, and extracted with ether. Removal of the solvent yielded a residue of crude benzhydrol (5 g.) which on crystallisation from light petroleum melted at 65—66°. When benzophenone was heated with an equimolecular quantity of potassium hydroxide in excess of methyl alcohol no reduction took place. When the methyl alcohol was replaced by *iso*propyl alcohol, however (3·64 g. of ketone, 20 c.c. of alcohol), reduction took place readily in the presence of a moderate excess of potassium hydroxide (1·20 g.); the crude benzhydrol, isolated by pouring the mixture into

water, was yellowish-brown, but after being dried and crystallised from light petroleum it was obtained as white needles (2·38 g.), m. p. 65—66°.

We are indebted to the Travis Trust for a generous gift of chemicals, and one of us (A. D. C.) acknowledges the tenure of a Junior Smeaton Research Scholarship and a Government Science Bursary.

UNIVERSITY OF OTAGO, DUNEDIN, NEW ZEALAND. [*Received, December 17th*, 1947.]

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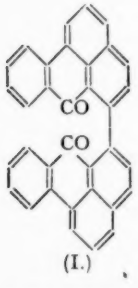
353. *Kationoid Reactivity of Aromatic Compounds. Part VIII. The Action of Fused Potassium Hydroxide on* 6 : 6′-*Dimesobenzanthronyl and a Note on the Properties of* 6- *and* 8-*Chloromesobenzanthrones.*

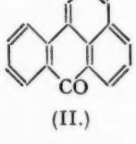
By W. BRADLEY and G. V. JADHAV.

6 : 6′-Di*meso*benzanthronyl reacts with potassium hydroxide at 240—250° to form a mixture of acids together with some violanthrone and an unidentified product. At 260—270° the principal product is violanthrone, the mode of formation of which is discussed. A further illustration of the ease of transmission of effects through the naphthalene nucleus of *meso*benzanthrone has been encountered in the reactivity of 6-chloro*meso*benzanthrone towards sodium methoxide and amines in circumstances which leave 8-chloro*meso*benzanthrone unaltered.

IN continuation of previous work further experiments have been carried out on the properties of 6 : 6′-di*meso*benzanthronyl (I). Unlike *meso*benzanthrone (II) which yields 4 : 4′-di*meso*benzanthronyl (III) (Lüttringhaus and Neresheimer, *Annalen*, 1929, **473**, 259), 6 : 6′-di*meso*benzanthronyl is completely stable towards concentrated alcoholic potassium hydroxide at 100—105°. It is unaffected by concentrated aqueous potassium hydroxide at 180—190°, but at 240—250° a mixture of acids is formed together with a smaller proportion of violanthrone and another unidentified product. The most abundant constituent, which is also the acid of highest melting point, is easily separable because of its sparing solubility in glacial acetic acid. Its elementary composition and melting point suggest the molecular composition, $C_{34}H_{22}O_4$. The structure may be (IV) in agreement with the known mode of scission of analogous ketones, but a dihydroxy-derivative of (I) is not improbable on present evidence. 1 : 1′-Dianthraquinonyl (V) forms a mixture of benzoic and diphenyl-3 : 3′-dicarboxylic acids when it is fused with potassium hydroxide at 200° (Eckert, *Ber.*, 1925, **58**, 321), and both α- and β-benzoylnaphthalene yield naphthalene and benzoic acid when they are heated with soda–lime at 350° (Grucarevic and Merz, *Ber.*, 1873, **6**, 1246). A mixture of α- and β-chrysenic acids (VII and VIII, respectively) is obtained by the alkali fusion of chrysoketone (VI), the α-form having the higher melting point and the lower solubility in aqueous acetic acid (Graebe, *Ber.*, 1900, **33**, 680).



(I.)



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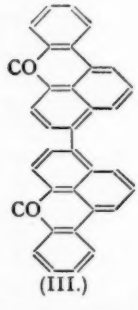

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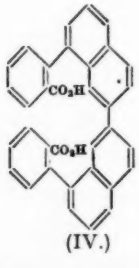

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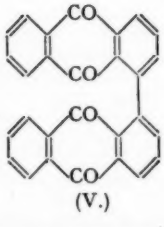


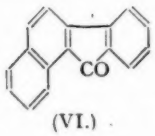
(V.)

Unsuccessful efforts have been made to cyclise the acid by treatment with sulphuric acid, oleum, and phosphorus pentachloride followed by aluminium chloride, procedures which serve to convert α- and β-chrysenic acid into chrysoketone or *o*-(1-naphthyl)benzoic acid into *meso*benzanthrone (Graebe, *loc. cit.*; Schaarschmidt and Georgeacopol, *Ber.*, 1917, **50**, 1082).

Crystallisation of the acetic acid-soluble portion of the acidic product gives a *substance*, m. p. 258—260°, the composition of which approximates to $C_{34}H_{22}O_5$. It may be a hydroxy-derivative of (IV), or a trihydroxy-derivative of (I). Its most characteristic property is that of dissolving in cold potassium hydrogen carbonate solution, forming a yellow solution with a green fluorescence.

At 260—270° the yield of acids is much smaller than at 240—250° and the product now

contains violanthrone (IX) as a principal constituent. The formation of this colouring matter has considerable interest since it involves the breaking of the 6 : 6′-linkage of the di*meso*benzanthronyl. The reconstruction of the molecule is not a purely thermal phenomenon because boiling with quinoline or diphenyl sulphone (b. p. 375°) for several hours leaves 6 : 6′-di*meso*benzanthronyl completely unchanged. Anhydrous aluminium chloride reacts to form a red oxonium salt, but there is no formation of violanthrone at 232° or at a lower temperature.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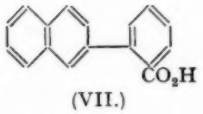
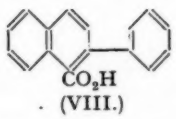

(VII.)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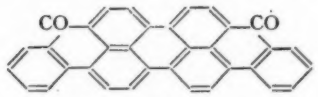
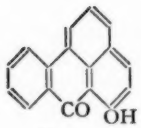
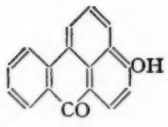
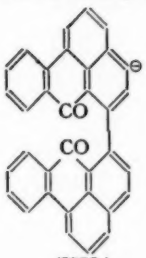
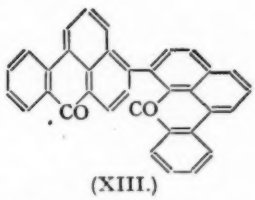

(IX.)

It is probable that the formation of violanthrone involves the intermediate production of 4 : 4′-di*meso*benzanthronyl which then undergoes cyclisation. We have confirmed that 4 : 4′-di*meso*benzanthronyl readily yields violanthrone at 200—210° (Lüttringhaus and Neresheimer, *loc. cit.*, state that the reaction begins at 170°), which is well below the temperature of the formation of the colouring matter from the 6 : 6′-isomeride. An idea that 6 : 6′-di*meso*-benzanthronyl is first hydrolysed to a mixture of *meso*benzanthrone and its 6-hydroxy-derivative (X), the former of which then yields violanthrone, is untenable because 6-hydroxy*meso*benzanthrone, although very stable to alkalis (*J.*, **1937**, 1791), is not encountered. Further, the reaction product contains no trace of 4-hydroxy*meso*benzanthrone (XI), which is easily recognised by the strong green fluorescence of its alkaline solution. This phenol invariably accompanies the products of transformation of *meso*benzanthrone in hot alkaline solution; in our experiments 5 mg. of *meso*benzanthrone were detected quite readily by this test.


(X.)


(XI.)


(XII.)


(XIII.)

The need of a strong alkali and a high temperature suggests that 6 : 6′-di*meso*benzanthronyl, like *meso*benzanthrone (see Part VII), is a very weak acid yielding the anion (XII), and that 4 : 4′-di*meso*benzanthronyl is formed from this by a cationotropic change in which the migrating *meso*benzanthronyl group either yields 4 : 6′-di*meso*benzanthronyl (XIII) at an intermediate stage or, more probably, rearranges during migration and forms 4 : 4′-di*meso*benzanthonyl directly.

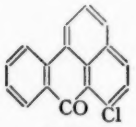
The mobility of a group attached to the 6-position of *meso*benzanthrone is a further consequence of the great intensity of the effect transmitted from the carbonyl group through the naphthalene unit of the structure. The same effect is responsible for the unusual ease with which *meso*benzanthrone undergoes substitution by electron-donating agents (see Part VI), for the ease with which the acyl derivatives of 3-, 4-, and 6-amino*meso*benzanthrone form salts with alkalis (Bradley, *J. Soc. Dyers Col.*, **1942**, **58**, 4), and for the facile hydrolysis of 6 : 6′-di*meso*benzanthronylamine (Part VI).

This property of *meso*benzanthrone has been studied further by comparing the ease of replacement of chlorine when substituted at the 6- and the 8-position successively. It has been found that, whilst the halogen of 6-chloro*meso*benzanthrone can be replaced quite readily by treatment with sodium methoxide or with a variety of aliphatic and aromatic amines, including *p*-nitroaniline, yet that of 8-chloro*meso*benzanthrone is stable towards these reagents.

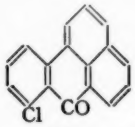
All the 6-arylamino*meso*benzanthrones form salts when 20% ethyl-alcoholic potassium hydroxide is added to their solutions in pyridine (cf. *ibid.*, p. 2), an additional illustration of the strong electron-attracting properties of the *meso*benzanthrone structure at the 6-position.

6-Chloro*meso*benzanthrone (XIV) has already been described and oriented (Part VII). 8-Chloro*meso*benzanthrone (XV) was prepared by reaction of 1-chloroanthr-9-one (Barnett and Matthews, *J.*, **1923**, **123**, 2549) with glycerol and sulphuric acid, a method which might yield either

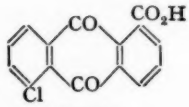
6- or 8-chloro*meso*benzanthrone or both of these. Actually, a homogeneous chloro*meso*benzanthrone, m. p. 178—179°, was obtained together with a substance, m. p. 120—121°, which appeared to be a eutectic mixture of the two isomers. The compound of m. p. 178—179° was different from 6-chloro*meso*benzanthrone, and its identity as 8-chloro*meso*benzanthrone was established by its conversion by oxidation into 5-chloroanthraquinone-1-carboxylic acid (XVI), m. p. 312—313° (Heilbron, Heslop, and Irving, *J.*, 1936, 784, give m. p. 312—313°, and Cahn, Jones, and Simonsen, *J.*, 1933, 444, m. p. *ca.* 306°, varying with the rate of heating).



(XIV.)



(XV.)



(XVI.)

A compound, m. p. 183°, has been referred to as 8-chloro*meso*benzanthrone (B.P. 301,197) but no proof of structure is given.

Experimental.

Fusion of 6 : 6′-*Di*meso*benzanthronyl with Potassium Hydroxide at* 240—250°.—6 : 6′-Di*meso*benzanthronyl (1·0 g.) was added portionwise to a stirred melt of potassium hydroxide (20 g.) and water (4 c.c.) at 240—250°, and the heating was then continued for 2 hours. The cooled melt, added to water, gave a solid and a red solution. The filtered solution showed a slight green fluorescence, and when acidified gave a yellow precipitate. This was collected, washed, and extracted by means of warm sodium hydrogen carbonate solution, and the acids were reprecipitated, giving 0·16 g. of material, m. p. 230—320°. Several repetitions of the experiment gave additional amounts of similar products. These were combined and extracted with boiling glacial acetic acid. A portion remained undissolved; this was insoluble in the common solvents with the exception of pyridine, from which it crystallised as the free *acid* (IV), m. p. above 360° (Found: C, 81·7; H, 3·9. Found, after washing with dilute hydrochloric acid, then water, and drying: C, 82·3; H, 4·7. $C_{34}H_{22}O_4$ requires C, 82·6; H, 4·5%). The acetic acid-soluble portion of the product was recrystallised several times from 50% acetic acid giving a *substance*, m. p. 258—260° (Found: C, 80·9; H, 4·3. $C_{34}H_{22}O_5$ requires C, 80·0; H, 4·4%). Increasing the time of fusion did not lead to an increase in the yield of acids. In one experiment the character of the non-acidic portion of the product was examined; it consisted of crude violanthrone (0·11 g.) and of a substance insoluble in alkali or a mixture of sodium hydroxide and sodium hyposulphite (dithionite) (0·55 g.). Weakly alkaline solutions of both acids give first a brownish-red coloration and then a reddish-brown precipitate on addition of a solution of diazotised *p*-nitroaniline. Similarly, the yellow, flocculent, freshly precipitated acids are rendered reddish-brown when diazotised *p*-nitroaniline is added to their weakly acid suspensions.

The acid of higher m. p. was recovered unchanged when its solution in cold, concentrated sulphuric acid was kept for several days and then added to water. No re-formation of 4 : 4′-di*meso*benzanthronyl occurred when the lower-melting acid was treated similarly, or when the acid of higher m. p. was warmed with 80% sulphuric acid for 3 hours at 60—70°, or when the same acid was heated at 140° in nitrobenzene solution with a molecular proportion of phosphorus pentachloride for 2 hours and then at 40° for an hour with the addition of 4 molecular proportions of anhydrous aluminium chloride. The higher-melting acid was sulphonated by cold, 20—25% oleum.

Fusion of 6 : 6′-*Di*meso*benzanthronyl with Potassium Hydroxide at* 260—270°.—The quantities and procedure employed in the experiment at 240—250° were adopted, the heating being maintained for 2·5 hours. The cooled melt, added to water, gave a colourless and non-fluorescent alkaline solution (absence of 2-hydroxy*meso*benzanthrone) from which only a negligible amount of acidic material separated when it was acidified by adding hydrochloric acid.

The alkali-insoluble portion of the product was blue. It was extracted first with water and then with benzene, and the benzene solution was evaporated and the absence of 6-hydroxy*meso*benzanthrone confirmed by applying the boroacetate test (*J.*, 1937, 1791). The benzene-insoluble material was further extracted with acetone, giving a solution which contained only a trace of violanthrone. The acetone-insoluble residue was dried and then digested at 70—80° with 10% sodium hydroxide solution containing sodium hyposulphite (dithionite). A blue-violet and then a deep violet-red solution formed quickly; it exhibited an intense brownish-red fluorescence. The solution was separated and the residue again treated with alkaline hyposulphite (dithionite) until nothing more dissolved; a dark blue residue (0·35 g.) remained. The combined extracts were filtered and then aerated, giving 0·4 g. of crude violanthrone.

Another experiment in which the period of fusion was 3 hours gave alkali-soluble products (0·04 g.), crude violanthrone (0·46 g.), and non-vattable residue (0·26 g.).

The crude violanthrone was purified by crystallisation from quinoline, giving an almost black powder, m. p. above 360° (Found: C, 87·1; H, 3·8. Calc. for $C_{34}H_{16}O_2$: C, 89·5; H, 3·5%), the properties of which were identical with those of a sample of violanthrone provided by Messrs. I.C.I. (Dyestuffs) Ltd., which had been purified similarly. In particular, it was almost completely insoluble in hot xylene, the faintly violet solution was bluish-violet, becoming violet-red as the concentration was increased, and all solutions exhibited a fluorescence. It dissolved readily in cold, concentrated sulphuric acid, forming a violet solution. Its reduced form obtained by treatment with alkaline sodium hyposulphite (dithionite) was easily soluble in dilute sodium hydroxide and showed very high affinity for cotton. In almost all of these respects it differed from *iso*violanthrone, which is more sparingly soluble in xylene and pyridine and

forms a green solution in cold, concentrated sulphuric acid, and whose reduced form is much less soluble in sodium hydroxide solutions.

The residue insoluble in alkaline sodium dithionite was a dark blue powder almost completely insoluble in boiling pyridine, and only slowly dissolved by cold, concentrated sulphuric acid, forming a violet solution. When it was boiled with a mixture of pyridine, 20% sodium hydroxide, and sodium dithionite the pyridine acquired a green colour and a yellow fluorescence. A solid separated on cooling, leaving the pyridine solution pink; the green colour was restored on heating. In the same circumstances *iso*violanthrone forms first a violet and then a green solution, whilst violanthrone and the vattable product of the present experiments behave identically, giving first a violet and then a blue colour to the pyridine.

8-*Chloro*meso*benzanthrone*.—Glycerol (8 g.) and 1-chloroanthr-9-one (10 g.) were added to a solution of concentrated sulphuric acid (10 c.c.) in water (20 c.c.) and the mixture was heated at 140—150° for 3 hours. A violet colour developed; later, sulphur dioxide was evolved and a dark solid separated. Water was added to the cooled product and the solid was collected, washed with water, and dried. A tacky product was obtained when the solid was extracted by means of chloroform and the solvent was evaporated from the filtered extract. This became granular when it was washed with light petroleum, and a residue, m. p. 173—175°, remained when it was repeatedly extracted by means of boiling dilute alcohol (75%). Crystallisation of the residue from alcohol gave yellow needles of (XV), m. p. 178—179° (Found: C, 76·9; H, 3·5; Cl, 13·3. Calc. for $C_{17}H_9OCl$: C, 77·1; H, 3·4; Cl, 13·4%). Evaporation of the dilute alcohol extracts gave a solid, m. p. 85—110°, which was raised only very slowly by repeated crystallisation from alcohol. Ultimately a substance, m. p. 120—121°, was obtained, evidently a eutectic of (XIV) and (XV) (Found: C, 77·4; H, 3·4; Cl, 12·5%).

5-*Chloroanthraquinone*-1-*carboxylic Acid*.—A solution of chromium trioxide (1 g.) in 50% acetic acid (5 c.c.) was added to a suspension of the above chloro*meso*benzanthrone, m. p. 178—179° (0·5 g.), in glacial acetic acid (10 c.c.) and the mixture was boiled for four hours. Water was added to the product, and the precipitated solid was collected, washed, extracted with warm dilute ammonia solution, and the extract filtered and acidified. A precipitate formed which crystallised from glacial acetic acid in almost colourless needles, m. p. 312—313° (Found: C, 62·7; H, 2·7; Cl, 12·4. Calc. for $C_{15}H_7O_4Cl$: C, 62·8; H, 2·5; Cl, 12·4%).

Action of Sodium Methoxide and of Amines on 8- *and* 6-*Chloro*meso*benzanthrone*.—8-Chloro*meso*benzanthrone was recovered almost completely unchanged when 0·5 g. was boiled for 3 hours with either aniline (2 g.) or monomethylaniline (1·5 g.), or when 0·2 g. was boiled for 7 hours with a solution of sodium methoxide prepared from sodium (1 g.) and methanol (10 c.c.).

6-*Methylamino*meso*benzanthrone*. A suspension of 6-chloro*meso*benzanthrone (0·5 g.) in 10 c.c. of 33% aqueous methylamine was heated at 180—190° for 7 hours. The *product* was cooled and then mixed with water. The solid was collected, washed, and recrystallised from alcohol. It formed orange-yellow needles, m. p. 160—161° (Found: C, 83·7; H, 5·0; N, 5·8. $C_{18}H_{13}ON$ requires C, 83·4; H, 5·1; N, 5·4%), which dissolved in pyridine with a yellow colour unaltered by the addition of a few drops of 20% ethyl-alcoholic potassium hydroxide.

6-*Anilino*meso*benzanthrone*. A solution of 6-chloro*meso*benzanthrone (0·5 g.) in 2·5 g. of freshly distilled aniline was boiled for 4 hours. A red solution resulted from which a yellow solid separated on cooling. The product was warmed with excess of dilute hydrochloric acid, and the undissolved solid was collected, washed, and then crystallised from alcohol. It formed yellow needles, m. p. 156—157° (Found: C, 86·1; H, 4·7; N, 4·4. $C_{23}H_{15}ON$ requires C, 86·0; H, 4·7; N, 4·4%). A yellow solution of this *compound* in pyridine is rendered yellowish-orange when a drop of ethyl-alcoholic potassium hydroxide is added.

The following analogues of 6-anilino*meso*benzanthrone were prepared by similar means. (The statements enclosed within parentheses refer to the colour changes which occur when a drop of ethyl-alcoholic potassium hydroxide is added to pyridine solutions of the several amines).

6-p-*Toluidino*meso*benzanthrone*, orange-yellow needles from alcohol, m. p. 131—132° (Found: C, 85·6; H, 5·0; N, 4·5. $C_{24}H_{17}ON$ requires C, 86·0; H, 5·1; N, 4·2%) (yellow to yellowish-orange). 6-p-*Chloranilino*meso*benzanthrone*, orange-yellow needles from nitrobenzene, m. p. 217—218° (Found: C, 77·5; H, 3·9; N, 4·1; Cl, 9·8. $C_{23}H_{14}ONCl$ requires C, 77·6; H, 4·0; N, 4·0; Cl, 10·0%) (yellow to pale orange-red, pink in thin layers). 6-p-*Nitroanilino*meso*benzanthrone*, orange needles from nitrobenzene, m. p. 293—294° (Found: C, 75·6; H, 3·9; N, 7·8. $C_{23}H_{14}O_3N_2$ requires C, 75·4; H, 3·9; N, 7·6%) (yellow to intense blue). 6-*α*-*Naphthylamino*meso*benzanthrone*, yellow needles from nitrobenzene, m. p. 243—244° (Found: C, 87·7; H, 4·7; N, 4·0. $C_{27}H_{17}ON$ requires C, 87·3; H, 4·6; N, 3·8%) (golden-yellow to deep reddish-orange). 6-*β*-*Naphthylamino*meso*benzanthrone*, red needles from nitrobenzene, m. p. 189—190° (Found: C, 87·2; H, 4·7; N, 3·7. $C_{27}H_{17}ON$ requires C, 87·3; H, 4·6; N, 3·8%) (golden-yellow to deep orange-red).

Hydrolysis of 6-*Chloro*meso*benzanthrone*.—6-Chloro*meso*benzanthrone (0·5 g.) was boiled with a solution prepared from sodium (2 g.) and methanol (20 c.c.) for 4 hours. Water and then dilute hydrochloric acid were added to the cooled product. The yellow precipitate was collected, washed, and then crystallised from glacial acetic acid. It gave yellow needles, m. p. 177—178°, alone or mixed with 6-hydroxy*meso*benzanthrone. Admixture with 6-chloro*meso*benzanthrone depressed the m. p. below 136°.

The experiments reported above were carried out in the Department of Applied Chemistry, College of Technology, Manchester. The authors are indebted to Prof. J. Kenner, F.R.S., who afforded facilities for the work, and thank the University of Bombay for the award of a Sir Mangaldas Nathubai Scholarship, and I.C.I. (Dyestuffs) Ltd. for a grant and gifts of intermediates.

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354. *The Solubility of Zinc Soaps in Organic Solvents.*

By (Miss) E. P. Martin and R. C. Pink.

The solubility of zinc soaps in organic solvents has been found to increase abruptly at a critical temperature. This increase is not due to an alteration in the degree of aggregation of the soap in solution but is a result of mesomorphic changes which occur in the solid soaps. Solution occurs at the critical temperature when solvent molecules penetrate between the hydrocarbon chains of the soap lattice. In discussing these results attention is drawn to the similarity between the structure of the metal soaps and materials of the high-polymer class.

For the present experimental study the zinc soaps were chosen for two main reasons. In the first place, some of the zinc soaps had been reported as differing from the majority of metal soaps in not exhibiting a plastic phase on heating (Lawrence, *Trans. Faraday Soc.*, 1938, **34**, 660), which suggested that their solutions might show points of interest. Secondly, the fact that the zinc soaps were known to have sharp melting points suitable for characterisation favoured accurate measurements. Much previous work in this field had for practical reasons been carried out with commercial grades of metal soaps which are well known to vary widely in composition, depending on the exact method of manufacture (cf. Elliott, "The Alkaline Earth and Heavy-metal Soaps", *Amer. Chem. Soc. Monograph*, 1946, **54**).

Lawrence (*loc. cit.*) prepared a wide variety of metal soaps, a number in a pure state for the first recorded time, and showed that they dissolved at sufficiently high temperatures in Nujol to give clear solutions which, in the majority of cases, set to gels on cooling. The zinc soaps were again found to be anomalous, no gelation occurring on cooling their solutions. Lawrence concluded that dispersion of the soaps in Nujol in the form of micelles resulted when the thermal agitation of the paraffin chains was sufficient to overcome the adhesion of the polar groups which were mainly instrumental in maintaining the crystal lattice. Gallay and Puddington (*Canadian J. Res.*, 1944, *B*, **22**, 161) noted a partial melting phenomenon with calcium stearate in various mineral oils at about 100°, the soap dissolving rapidly above this temperature, and Mardles and Clark (General Discussion on Swelling and Shrinking, Faraday Society, 1946) have shown that the swelling of sodium stearate powder in a mineral oil increases very markedly at about 70°, which corresponds with the temperature at which a mesomorphic change occurs in the solid soap.

Definite investigations on the existence of micelles in metal soap solutions in organic solvents have only been reported on a few occasions. Soyenkoff (*J. Physical Chem.*, 1930, **34**, 2519) carried out a careful study of nickel and iron soaps in benzene, from which it was concluded that particles of colloidal dimensions were present. It was difficult to explain the stability of the dispersions; ions were shown to be absent by measurement of the conductivity of the solutions. Bhatnagar, Kapur, and Hussain (*Proc. Indian Acad. Sci.*, 1939, **9**, *A*, 143) found that zinc oleate gave a negligible depression of the freezing point of benzene, although from some measurements by the Rast method they concluded that the soap in camphor solution was unimolecular. [Elliott (*op. cit.*, p. 176) appears to misquote these authors as authority for the statement that zinc oleate is unimolecular in *benzene* solutions.]

Palit and McBain (*J. Soc. Chem. Ind.*, 1947, **66**, 3; cf. Gonick, *J. Colloid Sci.*, 1946, **1**, 393) have investigated hexanolamine oleate solutions in benzene and concluded that the micelles in the absence of water had an average size of 3—4 molecules, increasing to a very large size when water was added to the system.

Experimental.

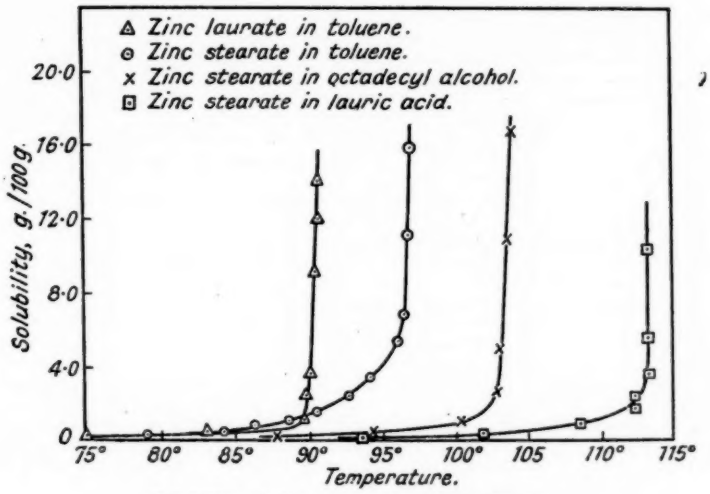
Preparation and Purification of Materials.—The acids used were decoic, lauric, myristic, and stearic. Pure samples of the first three acids were available (lauric and myristic acids were pre-war samples of Kahlbaum's "purissimus" grade) which were recrystallised from alcohol before use. Stearic acid was obtained from the B.D.H. purified grade *via* the methyl ester and subsequent fractional crystallization of the acid from alcohol until the m. p. rose to 69·2°. From these acids the soaps were prepared by the simple method already described (Pink, *J.*, 1938, 1252) and were dried in a vacuum-oven at 105°. The m. p.s of the acids and soaps are shown below:

Decoic acid ...	31·0°	Myristic acid ...	53·5°	Zinc decoate...	130·0°	Zinc myristate...	128·0°
Lauric acid ...	44·4	Stearic acid.....	69·2	Zinc laurate ...	130·5	Zinc stearate ...	129·0

Towards the end of this investigation an attempt was made to distil the zinc soaps in a molecular still, since the comparatively low and sharp m. p.s suggested that the metal–carboxyl link in the soaps might be largely covalent rather than ionic in character. Nine hours' distillation of zinc stearate (distillation path 5 mm.; still temperature 133°; condenser temperature — 70°; vacuum 10^{-4} mm.) gave about 100 mg. of a product which melted at 126° (as against 129° for the original soap) and, since it contained zinc, was neither the ketone (m. p. 88°) nor the acid (m. p. 69·2°). Although the m. p. indicated that

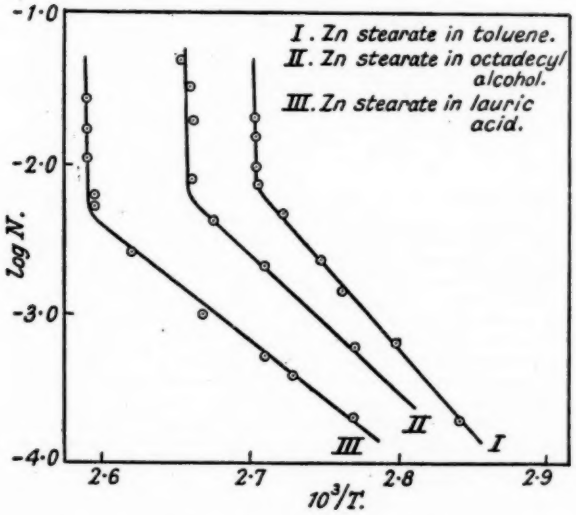
some decomposition (probably to the ketone) had occurred and that therefore the process, apart from the low yield, was not immediately available for purification, yet the fact that some zinc soap distilled provides further evidence for the covalent character of the metal–carboxyl link in these soaps. It may be noted that Bhatnagar, Kapur, and Hussain (*loc. cit.*) found zinc oleate solutions in benzene to be non-conducting, whereas magnesium oleate solutions in the same solvent were conductors, which may be regarded as additional evidence for the covalency of this link in the zinc soaps. Investigation of the possibility of using molecular distillation for purification of the soaps is continuing.

FIG. 1.



Solubility of zinc soaps in organic solvents.

FIG. 2.



Solubility Measurements.—The organic solvents employed were: toluene, b. p. 110·0—110·1°; xylene (mixture of isomers), b. p. 137—138°; *n*-octadecyl alcohol, m. p. 58·0°; lauric acid, m. p. 44·4°; nitrobenzene, b. p. 208—209°.

Measurements of solubility were made by a method similar to that described by Adam and Pankhurst (*Trans. Faraday Soc.*, 1946, **42**, 523) for measurements with aqueous solutions of paraffin-chain salts. The results with zinc laurate and stearate in toluene and zinc stearate in *n*-octadecyl alcohol and lauric acid are shown in Fig. 1, and the corresponding Hildebrand plots for the stearate are shown in Fig. 2.

In each case it will be seen that, after a slow rise in solubility, there is a sudden increase over a very small temperature range. The temperatures at which this occurs (the critical solution temperature or C.S.T.) for these cases and for the other solutions examined are shown in Table I. In this table the C.S.T. is taken arbitrarily to be the temperature at which a solubility of 10 g./100 g. of solvent is reached.

TABLE I.

Critical solution temperatures of zinc soaps in organic solvents.

	Toluene.	Xylene.	Octadecyl alcohol.	Lauric acid.	Nitrobenzene.
Zinc decoate	86·0°	89·0°	—	—	—
Zinc laurate.....	90·8	93·7	—	—	111·0°
Zinc myristate	93·0	96·0	108·0°	114·0°	113·0
Zinc stearate	97·0	98·5	104·0	113·0	112·0

but owing to the steep rise in solubility little difference would be made by taking another arbitrary basis provided the concentration chosen was sufficiently high. In all the solvents, dispersion of the soap occurs very rapidly at the C.S.T., and particularly at the high concentrations, no difficulty is experienced in determining this point. Separation of the soap in a very finely divided form occurs below the C.S.T. In no case was gelation of the soap solutions observed. The behaviour of solutions in nitrobenzene was unusual. When solutions in this solvent were heated above the m. p. of the soap, it separated, not as a solid, but as a finely divided emulsion which settled out on standing as a gelatinous mass obviously containing much nitrobenzene. The reasons for this behaviour will be discussed later. No similar phenomenon was observed with the other solvents.

Molecular-weight Measurements.—By analogy with the Krafft phenomenon in aqueous soap solutions, it seemed possible that this steep rise in solubility over a small temperature range might be due to a change in the degree of dispersion of the soap from molecular to micellar at the C.S.T. In order to settle this point, molecular-weight measurements of some of the soaps in toluene were made. A twin Cottrell apparatus (cf. Pearce and Hicks, *J. Physical Chem.*, 1926, **30**, 1678) was employed in which the difference in b. p. between the solutions and the pure solvent could be measured with an accuracy of $\pm$ 0·001° by means of a multi-junction copper–constantan thermocouple. The results of these measurements are shown in Table II. Some values for copper stearate are included for comparison. In agreement with previous work on organic solvents, micelles were found to be present at all concentrations examined. The apparent increase in micellar weight observed in the more concentrated solutions may be due to non-ideality of the solutions rather than to an increase in micellar size, although the fact that very concentrated solutions (> 10%) show faint opalescence indicates that at any rate in these concentrated solutions some micelles of a larger size are present. The micellar weights measured are probably mean values and do not necessarily indicate the absence of single molecules or of aggregates of smaller or larger size. Measurements could not be made above the concentrations shown in Table II

TABLE II.

Micellar weights of soaps in toluene.

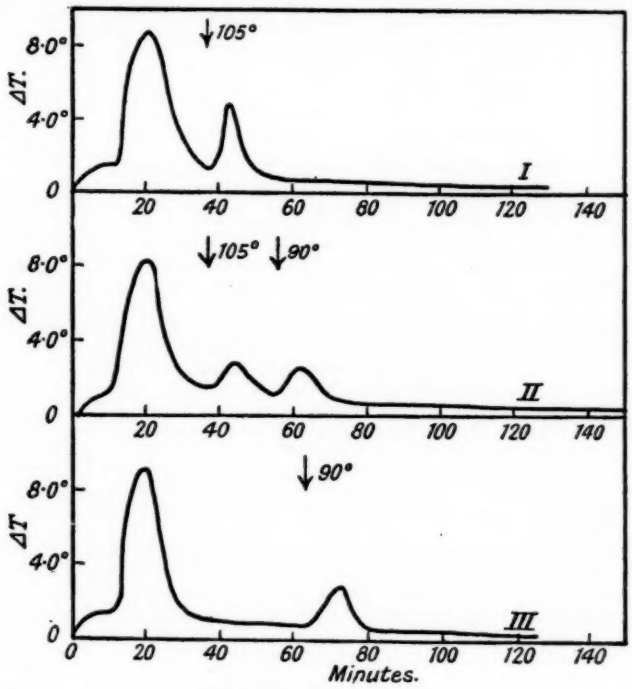
(C = concn. in g./100 g.; M = micellar weight; N = number of molecules per micelle.)

Zinc laurate.			Zinc stearate.			Copper stearate.		
C.	*M.*	*N.*	*C.*	*M.*	*N.*	*C.*	*M.*	*N*
0·653	2310	4·98	0·938	3460	5·47	1·038	4040	6·41
1·335	2840	6·13	1·690	3400	5·38	1·647	4220	6·70
1·935	3040	6·56	2·650	3530	5·58	2·580	4470	7·10

because of the incidence of foaming, which prevented the attainment of steady boiling temperatures in the solutions. Although the full concentration range in which the solubility of zinc stearate rapidly increases was for this reason not covered in the b. p. measurements, yet it is clear that with both the laurate and the stearate the increase in solubility observed at the critical temperature is not due to a change in aggregation of the soap from molecular to micellar.

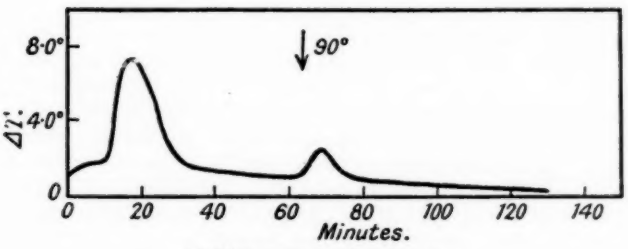
Phase Changes in the Solid Soaps.—Although zinc stearate and oleate had been reported by Lawrence (*loc. cit.*) as normal-melting substances, an investigation of the solid soaps by a cooling technique was undertaken in order to find out whether the steep rise in solubility could be attributed to a change in crystal structure at the critical temperature. It was found that, although zinc stearate showed no breaks in its cooling curve, the laurate and decoate had well-marked arrests in the temperature region in which the increase in solubility occurred (Figs. 3 and 4). In the case of zinc myristate a transition involving a very small heat change was observed at 73° (Fig. 5). Differential cooling curves were obtained in the following way. A sample of the soap contained in a Pyrex tube immersed in a mechanically stirred glycerol-bath was heated just above its fusion point and the difference in temperature between the cooling soap and the bath was measured by means of a ten-junction copper-constantan thermocouple, the junctions of which were dispersed as uniformly as possible throughout the sample. A difference in temperature between the soap and the bath of 0·002° could readily be observed by this arrangement, the large number of junctions ensuring that the maximum heat effect was measured : this is important because the thermal conductivity of the soaps is very low. The rate of cooling was not exactly the same in all the experiments but was usually about 0·7° per minute in the region in which the arrests were observed. The transition temperature in the case of zinc laurate and decoate was found to be affected by the presence of moisture. A freshly precipitated sample of zinc laurate which contained about 18% by weight of water before melting in the bath showed a well-marked transition at 105° (Curve I, Fig. 3). After partial drying over calcium chloride two transition points were observed (Curve II) while a dry sample of the soap showed only the transition at 90·0° (Curve III). Samples dried either by heating in the vacuum-oven or by keeping them for some time just above their m. p. in the glycerol-bath always showed the transition at 90·0° even on repeated fusion and cooling, while freshly precipitated samples containing water showed the transition at 105°. Estimates of the heat changes of the various transitions

FIG. 3.



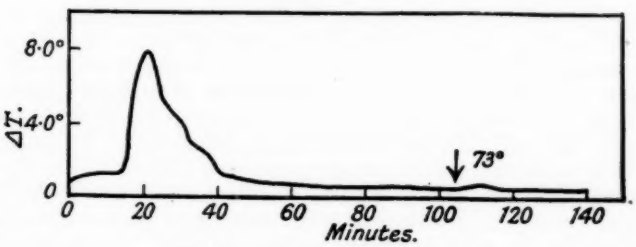
Cooling curves : zinc laurate.

FIG. 4.



Cooling curve : zinc decoate.

FIG. 5.



Cooling curve : zinc myristate.

were made by comparing the magnitude of the arrests with those obtained in the same apparatus with naphthalene and benzoic acid. The values obtained, with the corresponding entropy changes, are shown in Table III. The accuracy of the estimates relative to one another is about $\pm$ 5% but the absolute error may be greater than this.

TABLE III.

	ΔH_f.	ΔS_f.	$\Delta H_{105°}$.	$\Delta S_{105°}$.	$\Delta H_{90°}$.	$\Delta S_{90°}$.	$\Delta S_{(105°+90°)}$.	ΔS_{Total}.
Zinc laurate:								
Hydrated	15,000	37·2	3030	8·0	—	—	8·0	45·2
Partially dried	13,600	33·7	1870	4·9	1420	3·9	8·8	42·5
Anhydrous	12,900	32·0	—	—	2730	7·5	7·5	39·5
Lauric acid *	8,750	37·6	—	—	—	—	—	37·6
Stearic acid *	13,500	39·5	—	—	—	—	—	39·5

* Data from Int. Crit. Tables, First Ed., Vol. V, p. 134.

It will be noted that the total entropy of fusion of the anhydrous soap is approximately the same as the entropy of fusion of lauric and stearic acids, while the total entropy change for the transitions is approximately the same (*i.e.*, ~ 8 cals. deg.$^{-1}$ mole^{-1}) in all the samples, indicating a strong similarity between the processes involved in each case. The results indicate a different crystal arrangement in the presence and absence of water, and since the transition temperature is higher in the former case, it may be concluded that the low-temperature form is more stable in the presence of water. This is an unexpected result in view of the well-known effect of water in lowering the dispersion temperature of some other metal soaps in oils (Lawrence, *loc. cit.*). The explanation may be that the character of the metal–carboxyl bond in the dry soaps is predominantly covalent, and that the increased stability in the presence of water is due to the ionic nature of the lattice when water is present. There is no doubt that in some dry metal soaps this linkage is largely covalent as shown by their m. p.s lead oleate, for example, melts at 40° (Lawrence, *loc. cit.*). In all the curves, the first large arrest is that which occurs at the solidification point of the sample. It will be seen that the arrest observed with zinc myristate at the solidification point is of a complex type, containing at least two subsidiary arrests, indicating marked pre-melting a few degrees below the actual fusion point. It is possible that this pre-melting phenomenon involves the attainment of the same degree of freedom as that responsible for the arrests at 90° in the case of the decoate and laurate.

All the dry specimens of zinc laurate showed a further very small but reproducible arrest at about 98°, not shown in the curves. It was not clear whether this effect was due to a change in the zinc laurate crystals or to the presence of a small amount of impurity in the soap. The magnitude and position of the arrest were not affected by repeated crystallisation of the soap from toluene.

DISCUSSION.

The behaviour of the zinc soaps and their solutions, described above, is caused by the amphipathic nature of the soap molecules. Lawrence (*loc. cit.*) has pointed out that, at a temperature at which the hydrocarbon chains are in violent kinetic motion, the polar groups still adhere sufficiently strongly to maintain a rigid crystal lattice. *X*-Ray investigations have shown that the arrangement in the soap lattice is of layers of double molecules with the carboxyl groups contiguous (Harkins, Mattoon, and Corrin, *J. Amer. Chem. Soc.*, 1946, **68**, 220, who give references to earlier work of Hess, Gunderman, Philippoff, Kiessig, and Stauff).

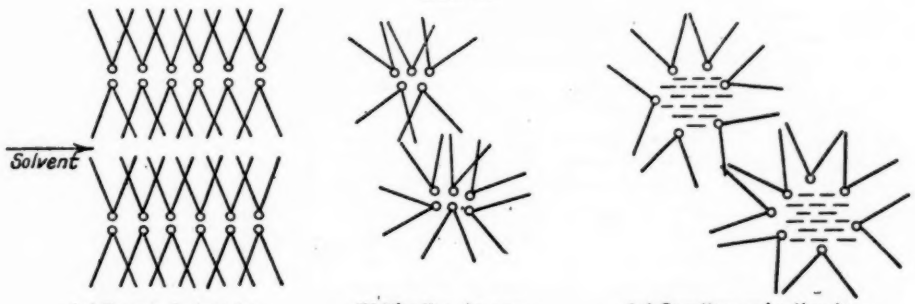
When the solid soap is heated, the thermal agitation of the hydrocarbon chains may be sufficient to bring about a change in the arrangement of the molecules in the lattice, resulting in a mesomorphic change of state. This is what occurs with the decoate, laurate, and myristate. With increasing chain length the effect becomes reduced, as shown by the smaller arrest observed with the myristate (C_{14}) as compared with the laurate (C_{12}) and decoate (C_{10}), while in the stearate, with eighteen carbon atoms in the chain, the attainment of the particular degree of freedom concerned is apparently postponed to the melting point. Zinc stearate is therefore a normal-melting substance. Polymorphism in the zinc soaps probably arises from variations in the angle of inclination of the hydrocarbon chains in the crystal lattice.

Solution in Non-polar Solvents.—When the soap is heated in presence of a solvent, the opening of the lattice, resulting from the thermal agitation of the chains, permits entry, between the chains, of solvent molecules provided the latter are of a sufficiently non-polar character, so that the heat of mixing with the hydrocarbon chains is small. The increased disorder in the lattice resulting from this penetration causes a breakdown of the rigid structure and dispersion of the soap in the form of micelles results. The reported insolubility of zinc stearate (Pink, *Trans. Faraday Soc.*, 1941, **37**, 181) in benzene is due presumably to the simple fact that its C.S.T. is above the b. p. of this solvent at atmospheric pressure. The process of solution is represented diagrammatically in Fig. 6, (*a*) and (*b*). In view of the size of the micelle in the solutions described in this paper, there is no *a priori* reason why its shape should not be spherical rather than the serpentine one suggested by Lawrence (*loc. cit.*). It should be noted that in the direction of the short spacing the hydrocarbon chains, above the C.S.T., have the structure of a liquid and not the regular arrangement shown in Fig. 6 (*a*).

Solution in Polar Solvents.—With relatively polar solvents such as lauric acid and *n*-octadecyl alcohol, the increased heat of mixing of the solvent with the hydrocarbon chains results in higher values for the C.S.T. as found experimentally (Table I). If the solvent is sufficiently

polar, as is the case with nitrobenzene, it can also penetrate between the polar end groups of the soap molecules when the lattice approaches its maximum degree of disorder near the fusion point. This results in swelling of the micelles [Fig. 6 (*c*)], and the soap separates, on cooling, as a swollen mass containing much nitrobenzene. A similar phenomenon has been reported recently by Schulman and McRoberts in oil–water–soap systems containing aliphatic alcohols or phenols (Faraday Soc. Discussion on Swelling and Shrinking, 1946). The slight solubility of the zinc soaps in both classes of solvent below the C.S.T. probably occurs by solution of single molecules which tend to aggregate into micelles simply because the micelle, having a more predominantly non-polar exterior than the molecule, is thereby a more soluble unit. In the micelle the molecules are held together by the strong attractive forces around their polar end groups. The existence of these forces is demonstrated by the tenacity with which the metal soaps hold on to water, and their presence explains the paradox of their simultaneous insolubility in water and ease of taking up water of hydration (cf. Pink, *J.*, 1938, 1252; Lawrence, *loc. cit.*). Mark (*Trans. Faraday Soc.*, 1947, **43**, 447) has recently discussed in detail the mechanical properties of high polymers in relation to structure, pointing out the extreme anisotropy of the lattice of, *e.g.*, rubber, which has strong chemical bonds along the parallel chains of isoprene units,

FIG. 6.



(*a*) Crystal lattice before penetration of solvent. (*b*) Micelles in non-polar solvent. (*c*) Swollen micelles in polar solvent.

but only weak van der Waals forces perpendicular to the chains. On rise of temperature the weak intermolecular bonds are severed while the strong chemical linkages along the chains remain unaffected. The parallel between this picture as drawn by Mark and the structure of the metal soaps is very striking, the chemical linkages of the isoprene units being replaced in the soaps by the strong dipole forces around the metal–carboxyl links. These links appear to be less strong in the zinc soaps than in, *e.g.*, the magnesium soaps, which in the solid anhydrous state have a brittle glassy character (Pink, *J.*, 1938, 1252) having a very strong outward resemblance to that of materials of the high-polymer class. When the temperature of the magnesium soaps is raised, no sharp melting point is observed; instead, a highly viscous liquid capable of being drawn into threads is obtained. As Mark has pointed out, the mutual attraction of van der Waals forces alone is insufficient to prevent slip of whole chains along one another, and so in the case of metal soaps such as magnesium oleate a viscous liquid rather than a rubbery solid is produced on melting. It would seem possible that by suitably altering the hydrocarbon end of the metal-soap chain, this slip might be minimised and materials with interesting mechanical properties might become available.

The authors wish to express their thanks to Professor A. R. Ubbelohde for many useful discussions and for his interest and advice throughout the work.

THE QUEEN'S UNIVERSITY, BELFAST. [*Received, December 19th*, 1947.]

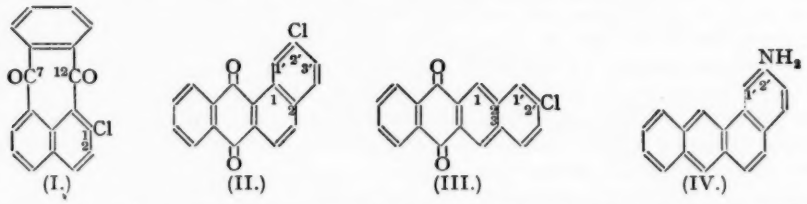
355. *Polycyclic Aromatic Amines. Part I.*

By G. M. Badger.

1-Chloropleiadene-7 : 12-dione (I) has been condensed with toluene-*p*-sulphonamide, and the product rearranged into 2′-*amino*-1 : 2-*benzanthraquinone*, which has been reduced to 2′-*amino*-1 : 2-*benzanthracene* (IV). The Friedel–Crafts reaction with 2-chloronaphthalene and phthalic anhydride has given two chloronaphthoylbenzoic acids, which have been cyclised to 2′-chloro-1 : 2-benzanthraquinone (II) and 3′-*chloro*-1 : 2-*benzanthraquinone*, respectively; (II) is evidently identical with the chlorobenzanthraquinone, described as 2′-chloro-2 : 3-benzanthraquinone (III), which Heller (*Ber.*, 1912, **45**, 665; 1913, **46**, 1497) obtained by the same series of reactions. 2′-Chloro-2 : 3-benzanthraquinone is still unknown.*

Experimental evidence that β-naphthylamine may be responsible for some of the cancers of the bladder to which operatives engaged in the manufacture of dye intermediates are somewhat liable has been provided by the production of such tumours in dogs by administration, over several years, of massive doses of β-naphthylamine. A variety of other types of tumour has also been produced in experimental animals by 2-aminofluorene, 2-acetamidofluorene, and 2-aminoanthracene (compare Bielschowsky, *Brit. Med. Bull.*, 1947, **4**, 382). It will be noted that in all these compounds the substituent is in a β-position of a fused-ring system. It seemed of interest to examine further compounds of this class, and in particular amino-derivatives of 1 : 2-benzanthracene, a hydrocarbon from which many of the known carcinogenic hydrocarbons are derived. The present communication describes the synthesis of 2′-*amino*-1 : 2-*benzanthracene* (IV).

1-Chloropleiadene-7 : 12-dione (I) is readily available (Fieser, *J. Amer. Chem. Soc.*, 1931, **53**, 3546), and may be rearranged, in good yield, by treatment with concentrated sulphuric acid, into 2′ chloro-1 : 2-benzanthraquinone (II) (Fieser and Fieser, *ibid.*, 1933, **55**, 3342). First attempts were therefore made to prepare the 2′-amino-compound from this chlorobenzanthraquinone by treatment with toluene-*p*-sulphonamide under conditions in which Ullmann and Fodor (*Annalen*, 1911, **380**, 317) converted 1-chloroanthraquinone into the corresponding toluene-*p*-sulphonamido-derivative, but no reaction occurred. Furthermore, 2′-*chloro*-1 : 2-*benzanthracene*, obtained from the quinone by reduction, was likewise recovered unchanged following the same treatment. 1-Chloropleiadene-7 : 12-dione, however, condensed readily with toluene-*p*-sulphonamide, 1-*toluene*-p-*sulphonamidopleiadene*-7 : 12-*dione* being isolated in satisfactory yield. Mild treatment with sulphuric acid gave 1-*aminopleiadene*-7 : 12-*dione*, the product of hydrolysis without rearrangement; but more vigorous treatment with concentrated sulphuric acid (compare B.P. 375,305) gave the deep purple 2′-*amino*-1 : 2-*benzanthraquinone*, the product of both hydrolysis and rearrangement. The constitution of this substance was proved by its conversion into the known 2′-hydroxy-1 : 2-benzanthraquinone (Fieser and Fieser, *loc. cit.*; Badger, *J.*, 1947, 940), by the method which Bachmann and Boatner (*J. Amer. Chem. Soc.*, 1936, **58**, 2194) used for the preparation of phenanthrols from the corresponding aminophenanthrenes. Reduction of the aminobenzanthraquinone with zinc dust and ammonia in the usual way gave the desired 2′-amino-1 : 2-benzanthracene (IV).



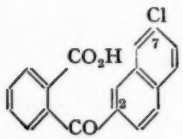
Fieser and Fieser (*loc. cit.*) have suggested that the chlorobenzanthraquinone which Heller (*loc. cit.*) obtained by cyclisation of the chloronaphthoylbenzoic acid resulting from the Friedel–Crafts reaction between 2-chloronaphthalene and phthalic anhydride, is not 2′-chloro-2 : 3-benzanthraquinone (III) but 2′-chloro-1 : 2-benzanthraquinone (II). At first Heller (*Ber.*, 1912, **45**, 665) considered his product to be 4-chloro-1 : 2-benzanthraquinone, but (*Ber.*, 1913, **46**, 1497) retracted this when he found that it gave an anthraquinonedicarboxylic acid on oxidation. Heller supposed this acid to be the 2 : 3-derivative but Fieser and Fieser (*loc.*

* *Added October 18th*, 1948.—Marschalk and Dassigny (*Bull. Soc. chim.*, 1948, **15**, 812), in a paper dated April 28th, 1948, have also studied the Friedel–Crafts reaction between 2-chloronaphthalene and phthalic anhydride. Their results (without experimental details) are similar to those reported here.

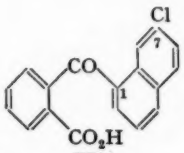
cit.) pointed out that the evidence given does not exclude the 1 : 2-dicarboxylic acid. In order to clarify this position the reaction between 2-chloronaphthalene and phthalic anhydride has been reinvestigated.

When carried out either in *s*-tetrachloroethane or in benzene solution a mixture of acids was obtained. Following the work of Heller, one of these was readily isolated in a fairly pure condition by recrystallisation of the crude product from acetic acid, the isomeric acids remaining in solution. In the present instance, further purification was achieved by the conversion of the acid into the *acetoxy-lactone*, followed by hydrolysis. This acid must be either 7-chloro-2-naphthoyl-*o*-benzoic acid (V) or 7-chloro-1-naphthoyl-*o*-benzoic acid (VI), for on cyclisation it gave 2′-chloro-1 : 2-benzanthraquinone (II), identical with a specimen prepared by rearrangement of 1-chloropleiadene-7 : 12-dione with concentrated sulphuric acid by the method of Fieser and Fieser (*loc. cit.*). It must be concluded therefore that Heller was in error in attributing the structure (III) to his product. It is of some interest that cyclisation of this chloronaphthoylbenzoic acid (V or VI) with molten aluminium chloride–sodium chloride also gave 2′-chloro-1 : 2-benzanthraquinone, for Weizmann, Bergmann, and Bergmann (*J.*, 1935, 1367) found that 1-*o*-naphthoylbenzoic acid rearranges under these conditions to give naphthacenequinone.

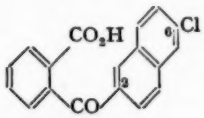
Heller (*loc. cit.*) isolated only one chloronaphthoylbenzoic acid from the mixture of crude acids, for attempts to purify the acids by recrystallisation of the free acid, or of its salts, were unsuccessful. In the present work the crude mixture obtained after the removal of the above isomeric acid was treated with acetic anhydride and pyridine, and a pure *acetoxy-lactone* was easily obtained by recrystallisation. Hydrolysis gave a *chloronaphthoylbenzoic acid*, which was converted into a *chlorobenzanthraquinone*. Only four chlorobenzanthraquinones could



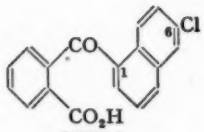
(V.)



(VI.)



(VII.)



(VIII.)

theoretically be obtained from 2-chloronaphthalene and phthalic anhydride. One is 2′-chloro-2 : 3-benzanthraquinone (III), and there are three 1 : 2-benzanthraquinones, namely, the 2′-, 3′-, and 4-chloro-derivatives. As the chlorobenzanthraquinone gave an alkaline vat without difficulty, and as the *chlorobenzanthracene* obtained from it by reduction was found to be colourless, 2′-chloro-2 : 3-benzanthraquinone would appear to be excluded, although evidence for its formation in small quantity, as a by-product of the cyclisation, was obtained. The 2′-chloro-1 : 2-benzanthraquinone structure was excluded by comparison with an authentic specimen. It was therefore concluded that the chlorobenzanthraquinone must be either the 3′- or the 4-chloro-isomer. It was found that no reaction took place with toluene-*p*-sulphonamide; the 4-isomer might be expected to react, for 1-chloroanthraquinone readily undergoes this reaction (Ullmann and Fodor, *loc. cit.*). In order to exclude the 4-isomer completely, the chlorobenzanthracene, obtained from the quinone by reduction, was converted into the corresponding *cyanobenzanthracene*, and hydrolysed to the *carboxybenzanthracene* by Newman and Orchin's method (*J. Amer. Chem. Soc.*, 1939, **61**, 244). This carboxybenzanthracene, and the *carboxybenzanthraquinone* obtained from it by oxidation, were found to differ from 1 : 2-benz-4-anthroic acid and 1 : 2-benzanthraquinone-4-carboxylic acid (Cook, *J.*, 1931, 2524). It must therefore be concluded that cyclisation of the second acid, which must have the structure (VII) or (VIII), gave 3′-chloro-1 : 2-benzanthraquinone.

The product obtained on reduction of the crude chlorobenzanthraquinone was bright yellow. This colour was evidently due to the presence of a small quantity of 2′-chloro-2 : 3-benzanthracene, for it was readily removed by a short treatment with maleic anhydride. Furthermore, the absorption spectrum of the crude product showed a band associated with a substituted 2 : 3-benzanthracene (see Clar, " Aromatische Kohlenwasserstoffe," Springer, 1941).

Experimental.

1-*Toluene*-p-*sulphonamidopleiadene*-7 : 12-*dione*.—A mixture of 1-chloropleiadene-7 : 12-dione (10 g., Fieser and Fieser, *loc. cit.*), toluene-*p*-sulphonamide (10 g.), anhydrous potassium carbonate (8 g.), copper acetate (0·4 g.), copper bronze (0·2 g.), and nitrobenzene (75 c.c.) was heated at 180—190° for 3½ hours. The nitrobenzene was removed in steam, and the residue recrystallised from acetic acid. 1-*Toluene*-p-*sulphonamidopleiadene*-7 : 12-*dione* (10·2 g.) formed small yellow plates, m. p. 211—213° (Found: C, 70·2; H, 4·1. $C_{25}H_{17}O_4NS$ requires C, 70·3; H, 4·0%).

1-*Aminopleiadene*-7 : 12-*dione*.—A mixture of the above toluene-*p*-sulphonamido-compound (1 g.) and concentrated sulphuric acid (10 c.c.) was kept at 30—40° for 1 hour, then poured into water; the product was collected and recrystallised from alcohol. 1-*Aminopleiadene*-7 : 12-*dione* (0·6 g.) formed orange-yellow prisms, m. p. 193—195° (Found: C, 79·3; H, 4·1. $C_{18}H_{11}O_2N$ requires C, 79·1; H, 4·0%).

2′-*Amino*-1 : 2-*benzanthraquinone*.—The above toluene-*p*-sulphonamido-compound (5 g.) was heated at 160° with concentrated sulphuric acid (50 c.c.) for ½ hour, and the solution poured into water. The yellow salt was collected and washed on the filter with dilute sodium hydroxide until it had all been converted into the purple base. 2′-*Amino*-1 : 2-*benzanthraquinone* formed long, shining, deep purple needles, from toluene, m. p. 204—205° (Found: C, 79·1; H, 4·0. $C_{18}H_{11}O_2N$ requires C, 79·1; H, 4·0%). The quinone gave a dark red-brown solution in concentrated sulphuric acid, and it readily gave a red-brown vat with alkaline hydrosulphite (dithionite).

Proof of constitution. A solution of 2′-amino-1 : 2-benzanthraquinone (2 g.) in pyridine (20 c.c.) was added dropwise, with stirring, to a mixture obtained by adding sodium nitrite (1·5 g.) to a mixture of water (7·5 c.c.) and sulphuric acid (15 c.c.). The temperature was kept below 5° during the addition. After 2 hours the mixture was diluted with a large volume of water, urea was added, and the whole heated until gas evolution ceased. The product was collected, sublimed at 230°/0·1 mm., and recrystallised from alcohol. It formed red crystals, m. p. 251°, not depressed by admixture with an authentic specimen of 2′-hydroxy-1 : 2-benzanthraquinone.

2′-*Amino*-1 : 2-*benzanthracene*.—Finely divided 2′-amino-1 : 2-benzanthraquinone (1 g.) was reduced by 12 hours' boiling with zinc dust (3 g.), ammonium hydroxide (*d* 0·880; 15 c.c.), and water (60 c.c.). The insoluble material was dried, and sublimed from the zinc at 180°/0·1 mm. In some runs the sublimate was purple, owing to unchanged quinone. This was removed by treatment with a boiling solution of sodium hydroxide–sodium hydrosulphite (dithionite), followed by rapid filtration. The residue was then washed, dried, and recrystallised from benzene. 2′-*Amino*-1 : 2-*benzanthracene* (0·6 g.) formed yellow plates, from benzene, m. p. 162·5—164·5° (Found: C, 88·8; H, 5·25. $C_{18}H_{13}N$ requires C, 88·9; H, 5·35%). Solutions of the amine were strongly fluorescent in daylight, and rapidly became dark if exposed to light and air.

Chloronaphthoylbenzoic Acids.—A mixture of 2-chloronaphthalene (12 g.), phthalic anhydride (11 g.), aluminium chloride (22 g.), and *s*-tetrachloroethane (100 c.c.) was allowed to stand in ice, with shaking, for 3 hours, and then at room temperature for 24 hours. Finally, the mixture was heated on a steam-bath for 1 hour. After decomposition with ice and hydrochloric acid in the usual way, the product was extracted with warm dilute sodium carbonate (charcoal), and the crude acid (23·6 g.) precipitated with hydrochloric acid. Recrystallisation from acetic acid (charcoal) gave *o*-7-chloro-1(or 2)-naphthoylbenzoic acid (V or VI) (3·6 g.), m. p. 216—218° (Heller gives m. p. 225—227° for the pure acid). A sample of the acid (1·4 g.) was converted into the *acetoxy-lactone* by heating on the steam-bath for 2 hours with pyridine (9 c.c.) and acetic anhydride (3·5 c.c.). It formed colourless prisms from alcohol, m. p. 168—170° (Found: C, 68·4; H, 3·7. $C_{20}H_{13}O_4Cl$ requires C, 68·1; H, 3·7%). The pure acid was obtained by hydrolysis of the lactone with alcoholic sodium hydroxide, followed by recrystallisation from acetic acid.

The liquors from the first acetic acid crystallisation of the crude product gave, on addition of water, a gummy acid which, after drying, was treated with pyridine (120 c.c.) and acetic anhydride (40 c.c.) for 2 hours on the steam-bath. After being poured into water, a brown gum was obtained, which crystallised on treatment with a little alcohol and benzene. After being washed with alcohol, the solid was recrystallised from alcohol (charcoal) and gave almost colourless crystals, m. p. 130—131° (7·4 g.). After further recrystallisation from alcohol and from benzene, the pure *acetoxy-lactone* formed colourless elongated prisms, m. p. 132—134° (Found: C, 68·3; H, 3·7. $C_{20}H_{13}O_4Cl$ requires C, 68·1; H, 3·7%). Hydrolysis of this acetoxy-lactone followed by recrystallisation from benzene gave o-6-*chloro*-2 (or 1)-*naphthoylbenzoic acid*, (VII) or (VIII), as colourless prisms, m. p. 174—175·5° (Found: C, 69·6; H, 3·7. $C_{18}H_{11}O_3Cl$ requires C, 69·6; H, 3·5%). Similar results were obtained when the Friedel–Crafts reaction was carried out in benzene solution.

2′-*Chloro*-1 : 2-*benzanthraquinone*.—A mixture of the above acid (m. p. 218°, 0·5 g.) and concentrated sulphuric acid (5 c.c.) was heated at 60—70° for 6 hours. The product, obtained as a bright yellow powder on pouring into water, was extracted with boiling sodium carbonate, washed, and recrystallised from acetic acid. 2′-Chloro-1 : 2-benzanthraquinone formed bright yellow needles, m. p. 235—236°, alone, or mixed with an authentic specimen prepared by Fieser and Fieser's method (*loc. cit.*). It readily gave a red vat with alkaline hydrosulphite. The same quinone was also obtained when the acid (1 g.) was cyclised by heating with aluminium chloride (10 g.) and sodium chloride (2 g.) for 1 hour at 140°.

2′-*Chloro*-1 : 2-*benzanthracene*.—A mixture of the quinone (5·2 g.), stannous chloride (5 g.), acetic acid (100 c.c.), and concentrated hydrochloric acid (30 c.c.) was refluxed for 1 hour, cooled, diluted with water, and the solid filtered off; it was refluxed with 2N-sodium hydroxide (100 c.c.) and zinc dust (10 g.) for 3 hours (Badger and Cook, *J.*, 1939, 802). 2′-*Chloro*-1 : 2-*benzanthracene* (4·02 g.) formed colourless plates from acetic acid, m. p. 161·5—162·5° (Found: C, 82·35; H, 4·3. $C_{18}H_{11}Cl$ requires C, 82·3; H, 4·2%).

The *picrate*, prepared in acetic acid with excess of picric acid, dissociated on attempted recrystallisation from acetic acid, but was recrystallised from benzene. It formed red needles, m. p. 166·5—167° (Found: C, 58·7; H, 2·7. $C_{24}H_{14}O_7N_3Cl$ requires C, 58·6; H, 2·85%).

3′-*Chloro*-1 : 2-*benzanthraquinone*.—A mixture of *o*-6-chloro-2 (or 1)-naphthoylbenzoic acid (m. p. 175°, 0·5 g.) was heated at 95° with concentrated sulphuric acid (5 c.c.) for 3 hours. Recrystallised from acetic acid, and from benzene, 3′-*chloro*-1 : 2-*benzanthraquinone* (0·35 g.) formed fine yellow needles, m. p. 213—215° (Found: C, 73·9; H, 3·15. $C_{18}H_9O_3Cl$ requires C, 73·9; H, 3·1%). It readily formed a red vat with alkaline hydrosulphite. A mixed m. p. with 2′-chloro-1 : 2-benzanthraquinone was *ca.* 180°.

3′-*Chloro*-1 : 2-*benzanthracene*.—The above chlorobenzanthraquinone (3·0 g.) was reduced by the stannous chloride–zinc and alkali method as described for the 2′-isomer. The crude product (1·9 g.) formed bright yellow plates from acetic acid, and showed a brilliant green-yellow fluorescence in ultra-

violet light, but its solution in benzene was not fluorescent. A semi-quantitative examination of the absorption spectrum showed an absorption band at 4775 A., as might be expected from a 2 : 3-benzanthracene derivative. The crude product, however, was readily decolourised by a few minutes' boiling with a little maleic anhydride in xylene solution, followed by the removal of the xylene with steam in the presence of dilute sodium hydroxide. There was no significant loss of material by this purification process. The pure 3′-*chloro*-1 : 2-*benzanthracene* formed colourless plates from acetic acid, m. p. 175—177° (Found : C, 82·25; H, 4·2. $C_{18}H_{11}Cl$ requires C, 82·3; H, 4·2%).

3′-*Cyano*-1 : 2-*benzanthracene*.—A mixture of 3′-chloro-1 : 2-benzanthracene (0·9 g.), cuprous cyanide (0·5 g.), acetonitrile (1 c.c.), and pyridine (3 c.c.) was heated in a sealed tube at 230—240° for 48 hours. The neutral product was purified by sublimation at 180°/0·1 mm. and formed fawn needles, m. p. 181·5—182·5° from acetic acid (yield 0·47 g.) (Found : C, 89·9; H, 4·6. $C_{19}H_{11}N$ requires C, 90·1; H, 4·4%). Its solutions showed an intense blue fluorescence in daylight. Oxidation of this *cyanobenzanthracene* (0·1 g.) with sodium dichromate (0·5 g.) in acetic acid (10 c.c.) gave 3′-*cyano*-1 : 2-*benzanthraquinone* as fine yellow needles, m. p. 307—308°, from acetic acid (Found : C, 80·6; H, 3·1. $C_{19}H_9O_2N$ requires C, 80·6; H, 3·2%).

3′-*Carboxy*-1 : 2-*benzanthracene*.—A solution of the above 3′-cyano-1 : 2-benzanthracene (0·25 g.) in acetic acid (35 c.c.) and 70% sulphuric acid (7 c.c.) was refluxed for 6 hours. The *acid* separated from acetic acid, or from xylene, as a microcrystalline powder, m. p. 290°, after darkening (Found : C, 83·7; H, 4·3. $C_{19}H_{12}O_2$ requires C, 83·3; H, 4·4%). A mixed m. p. with 1 : 2-benz-4-anthroic acid (m. p. 281°; Cook *J.*, 1931, 2524) was 240—250°. Oxidation of this carboxybenzanthracene (0·1 g.) with sodium dichromate (0·5 g.) in acetic acid (10 c.c.) gave 3′-*carboxy*-1 : 2-*benzanthraquinone*, as yellow microprisms, from tetrahydrofurfuryl alcohol, m. p. 345°, after darkening and sintering (Found : C, 75·3; H, 3·3. $C_{19}H_{10}O_4$ requires C, 75·5; H, 3·3%) [4-carboxy-1 : 2-benzanthraquinone has m. p. 292—293° (decomp.); Cook, *loc. cit.*].

The author thanks Mr. J. M. L. Cameron for the microanalyses. This work was carried out during the tenure of an I.C.I. Research Fellowship.

UNIVERSITY OF GLASGOW. [*Received, December 28th*, 1947.]

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356. *Synthetic Antimalarials. Part XXXI.* 2-p-*Chloroanilino*-4-β-*diethylaminoethylaminoquinazolines containing Various Substituents in the Quinazoline Nucleus.*

By F. H. S. CURD, J. K. LANDQUIST, and F. L. ROSE.

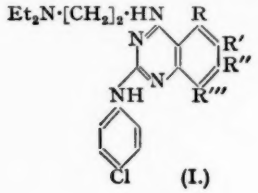
In continuation of the previous study of 2-arylamino-4-aminoalkylaminoquinazolines (Part XIV, *J.*, 1947, 775) as antimalarial agents the preparation of a series of 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazolines carrying various substituents (Cl, NO_2, NH_2, Me, OMe, and 6 : 7-benzo) in one or more positions of the quinazoline nucleus is now described. These new compounds were synthesised from the appropriately substituted 2 : 4-dihydroxyquinazolines through the corresponding 2 : 4-dichloroquinazolines and 2-chloro-4-β-diethylaminoethylaminoquinazolines (cf. Part XIV, *loc. cit.*). The required dihydroxyquinazolines were made by two general methods : (*a*) reaction of urea with a substituted anthranilic acid, and (*b*) reaction of sodium cyanate with a substituted anthranilic acid, ester, amide, or nitrile, and cyclisation of the resulting urea. By the first method the 7-nitro- and 6 : 7-benzo-compounds were prepared, and by the second the 6- and 7-chloro-, 7-nitro-, 7-methyl-, 5-, 6-, 7-, and 8-methoxy-, and 6 : 7-dimethoxy-derivatives.

THERE appeared to be two possible origins of the antimalarial activity of the 2-arylamino-4-aminoalkylaminoquinazolines described in Part XIV (*J.*, 1947, 775). On the one hand there was their relationship to the 2-arylamino-4-aminoalkylamino-6-methylpyrimidines described in Parts I and II (*J.*, 1946, 343, 351) and the corresponding 5-alkyl derivatives (Part VII, *ibid.*, p. 378) on which they were modelled. Alternatively, the previously observed activity of 4-γ-diethylaminopropylaminoquinazoline (see Part XVI, *J.*, 1947, 890) suggested that the 2-arylamino-group might not be concerned with the display of antimalarial activity, although this appeared less likely in view of the greater activity of 2-*p*-chloroanilino-4-γ-diethylaminopropylaminoquinazoline compared with that of the compound less the arylamino-group. In any event it was thought to be of interest to examine the effect of introducing substituents into the *benz*-ring of the quinazoline nucleus, and indeed it was thought that such an investigation might throw some light on the questions at issue, particularly when compared with the work described in Part XVI. The disclosure (B.P. Appln. 27673/38) of the influence of analogous substitution, for example of halogen in the 7-position of the 4-dialkylaminoalkylaminoquinolines, added further point to these researches.

Taking as the parent compound the active 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline (Part XIV, *loc. cit.*), the following substituents were therefore introduced into the quinazoline nucleus : 6- and 7-chloro-, 6- and 7-nitro- (also reduced to the 6- and 7-amino-),

7-methyl, 5-, 6-, 7-, and 8-methoxy-, 6 : 7-dimethoxy- and 6 : 7-benzo-. Reference to the table of activities shows, however, that none of the substituted compounds prepared was more active than the parent substance, and most were less.

The new compounds of type (I) were prepared by the first method worked out for this type of compound and reported in Part XIV, *viz.*, by interaction of the appropriately substituted 2 : 4-dichloroquinazoline with β-diethylaminoethylamine to give a 2-chloro-4-β-diethylaminoethylaminoquinazoline which was caused to react with *p*-chloroaniline. As in the case of the parent 2 : 4-dichloroquinazoline there was no evidence of the intermediate formation of any of the isomeric 4-chloro-2-β-diethylaminoethylaminoquinazolines.



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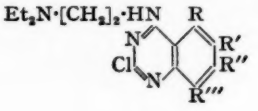

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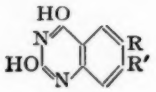

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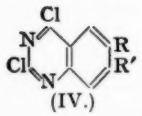

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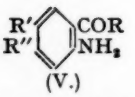

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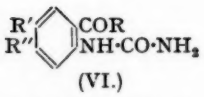


(VI.)

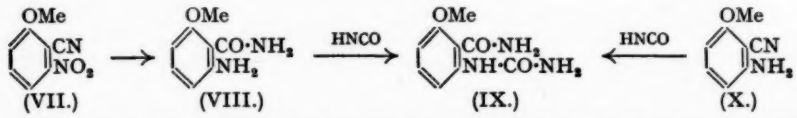
The established method of preparing 2 : 4-dichloroquinazoline involves treating 2 : 4-dihydroxyquinazoline with phosphorus pentachloride and phosphoryl chloride, and this procedure has been used for many of its derivatives described in this paper, although the use of phosphorus pentachloride was sometimes avoided by using phosphoryl chloride and dimethylaniline : this method of replacing hydroxyl groups by chlorine, found so convenient and widely applicable for pyrimidine compounds by Baddiley and Topham (*J.*, 1944, 679), promises to be equally valuable in the quinazoline series.

The various substituted 2 : 4-dihydroxyquinazolines were prepared as follows.

6-*Chloro*-2 : 4-*dihydroxyquinazoline* (III; R = Cl, R′ = H) was obtained by the action of sodium cyanate on methyl 5-chloroanthranilate (V; R = OMe, R′ = Cl, R″ = H) in acetic acid, followed by cyclisation of the resulting urea.

4-Chloroanthranilic acid (V; R = OH, R′ = H, R″ = Cl), prepared by a modification of Cohn's method (*Monatsh.*, 1901, **22**, 485), was treated with sodium cyanate to give (VI; R = OH, R′ = H, R″ = Cl) which, cyclised with alkali, afforded 7-chloro-2 : 4-dihydroxyquinazoline (III; R = H, R′ = Cl). 4-Nitroanthranilic acid, similarly prepared from 4-nitroacet-*o*-toluidide, furnished 7-*nitro*-2 : 4-*dihydroxyquinazoline* (III; R = H, R′ = NO_2) (*a*) by reaction with urea in boiling aqueous solution, and (*b*) by reaction with sodium cyanate to give 4-nitro-2-ureidobenzoic acid (VI; R = OH, R′ = H, R″ = NO_2) followed by cyclisation of this with boiling hydrochloric acid. 6-Nitro-2 : 4-dihydroxyquinazoline (III; R = NO_2, R′ = H) was prepared by nitration of 2 : 4-dihydroxyquinazoline (Bogert and Scatchard, *J. Amer. Chem. Soc.*, 1919, **41**, 2058).

2 : 4-Dihydroxy-7-methylquinazoline (III; R = H, R′ = Me), prepared previously by von Niementowski by heating 4-methylanthranilic acid or its amide with urea (*J. pr. Chem.*, 1889, **40**, 21) and by ring closure of ethyl 2-carboxyamido-5-methylphenylurethane (*ibid.*, 1895, **51**, 511), was obtained for the present work by the action of sodium cyanate on 4-methylanthranilic acid (V; R = OH, R′ = H, R″ = Me) or the corresponding amide followed by cyclisation of the intermediate 3-ureido-*p*-toluic acid (VI; R = OH, R′ = H, R″ = Me) and 3-ureido-*p*-toluamide (VI; R = NH_2, R′ = H, R″ = Me) respectively. It was also found to be the product of the action of sodium hydroxide or hydrochloric acid on 3-*ureido*-p-*tolunitrile*.



(VII.) (VIII.) (IX.) (X.)

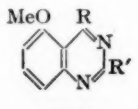
Catalytic reduction of 2-nitro-6-methoxybenzonitrile (Lobry de Bruyn, *Rec. Trav. chim.*, 1883, **2**, 210) in methanol using Raney nickel gave mainly 2-amino-6-methoxybenzamide which

with sodium cyanate in acetic acid gave 2-*ureido*-6-*methoxybenzamide*. The same product was formed from 2-amino-6-methoxybenzonitrile and sodium cyanate. This is surprising in view of the resistance of the nitrile group in this compound to hydrolysis by the usual methods (Friedländer, Bruckner, and Deutsch, *Annalen*, 1912, **388**, 41), and the fact that all *o*-aminobenzonitriles do not hydrolyse during reaction with cyanate. 3-Amino-*p*-tolunitrile, for example, gives 3-ureido-*p*-tolunitrile, and not the amide. Ring closure of (IX) with boiling 30% sodium hydroxide gave the required 2 : 4-*dihydroxy*-5-*methoxyquinazoline* (XI; R = R′ = OH).

2 : 4-Dihydroxy-6-methoxyquinazoline (III; R = OMe, R′ = H) was prepared from 5-methoxyanthranilic acid (V; R = OH, R′ = OMe, R″ = H) which was converted by reaction with sodium cyanate into 2-ureido-5-methoxybenzoic acid (VI; R = OH, R′ = OMe, R″ = H), followed by ring-closure with hydrochloric acid.

Whereas Mann and his co-workers (Part XVI, *loc. cit.*) prepared 2 : 4-dihydroxy-7-methoxyquinazoline by reaction of 4-methoxyanthranilic acid (V; R = OH, R′ = H, R″ = OMe) with cyanate and ring closure of the resulting 2-ureido-4-methoxybenzoic acid (VI; R = OH, R′ = H, R″ = OMe) with alkali, we have found it more convenient to proceed *via* the corresponding amide (VI; R = NH_2, R′ = H, R″ = OMe) which was cyclised with hydrochloric acid. The 2-ureido-4-methoxybenzamide was obtained from 4-methoxyanthranilamide (V; R = NH_2, R′ = H, R″ = OMe) which resulted, together with a smaller proportion of 2-amino-4-methoxybenzonitrile, from reduction of 2-nitro-4-methoxybenzonitrile with iron in alcohol.

2 : 4-Dihydroxy-8-methoxyquinazoline (XII; R = R′ = OH) was prepared by Froelicher and Cohen (*J.*, 1921, **119**, 1431) from 3-methoxyanthranilic acid (XIII; R = R′ = H) by



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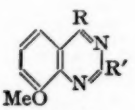

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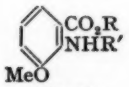

(XIII.)

reaction with sodium cyanate to give 2-ureido-3-methoxybenzoic acid (XIII; R = H, R′ = CO·NH_2) which was then ring closed by boiling with hydrochloric acid. We obtained better results by a variant of the process, starting with methyl 3-methoxyanthranilate (XIII; R = Me, R′ = H), converting it into methyl 2-ureido-3-methoxybenzoate (XIII; R = Me, R′ = CO·NH_2), and effecting the final ring closure merely by boiling with water.

Catalytic reduction of 6-nitroveratric acid in methanol solution over Raney nickel gave 6-aminoveratric acid which, without isolation, was caused to react with sodium cyanate to give 2-*ureido*-4 : 5-*dimethoxybenzoic acid* (VI; R = H, R′ = R″ = OMe). Treatment with sodium hydroxide gave 2 : 4-*dihydroxy*-6 : 7-*dimethoxyquinazoline* (III; R = R′ = OMe) accompanied by some hydrolysis of the ureido-group to 6-aminoveratric acid. This is the only instance, in this work, where such a hydrolysis was observed.

Antimalarial Activities.

·2-p-*Chloroanilino*-4-β-*diethylaminoethylaminoquinazolines.*

Ref. no.	Substituent.	Dose (mg./kg.).	Activity.	Ref. no.	Substituent.	Dose (mg./kg.).	Activity.
3756	—	40	+ to ++	3931	7-Methyl-	160	+ to ++
		20	−			80	+
4258	6-Chloro-	80	++			40	−
		40	+	5124	5-Methoxy-	80	±
3918	7-Chloro-	200	+ to ++	4624	6-Methoxy-	80	+ to ++
		40	−			40	+
4537	6-Nitro-	80	++			20	−
		40	+ to ++	3963	7-Methoxy-	120	+ to ++
4259	7-Nitro-	120	++			80	±
		80	±	4609	8-Methoxy-	160	+
		40	−			80	−
4544	6-Amino-	160	+ to ++	4185	6 : 7-Dimethoxy-	80	+ to ++
		80	+			40	±
4213	7-Amino-	160	+ to ++	3964	6 : 7-Benzo-	400	++
		80	+			200	+ to ++
						120	+

For the preparation of 2 : 4-*dichloro*-6 : 7-*benzoquinazoline* (IV; RR′ = benzo), which is mentioned without details of preparation or description in B.P. 288,159, 2 : 4-*dihydroxy*-6 : 7-

benzoquinazoline (III; RR′ = benzo) was required and resulted from the reaction of 2-naphthylamine-3-carboxylic acid with urea in boiling phenol solution.

The variously substituted 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazolines described in this paper have been tested for antimalarial activity by Dr. D. G. Davey of these laboratories, using *P. gallinaceum* in chicks. His results are summarised in the following table where the activities are expressed at various doses as in Part I (*loc. cit.*). The results obtained with the parent 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride (3756) are included for comparison. The actual preparation (base, dihydrochloride, or trihydrochloride) used for biological test is indicated in the experimental section where the reference numbers are given in the appropriate place.

Experimental.

6-Chloro-2 : 4-dihydroxyquinazoline (III; R = Cl, R′ = H).—Methyl 5-chloroanthranilate (20 g.) (prepared by the method of Freundler, *Bull. Soc. chim.*, 1911, **9**, 606; cf. Part XVI, *loc. cit.*) in acetic acid (100 c.c.) was treated with a suspension of sodium cyanate (11 g.) in water (50 c.c.) while stirring, and the mixture then kept overnight at room temperature. The crystalline product was filtered off, washed with water, and dissolved in hot water (6 l.) and 10N-sodium hydroxide (30 c.c.). The filtered solution was then acidified with acetic acid and the *6-chloro-2 : 4-dihydroxyquinazoline* filtered off, washed, and dried (yield, 14·5 g.); m. p. 345—348° (Found: Cl, 17·7. $C_8H_5O_2N_2Cl$ requires Cl, 18·1%).

2 : 4 : 6-Trichloroquinazoline (IV; R = Cl, R′ = H).—The preceding compound (14·5 g.), phosphorus pentachloride (30·65 g.), and phosphoryl chloride (15 c.c.) were heated under reflux until a clear solution was formed (5 hours). The phosphoryl chloride was then removed under reduced pressure, and the residue distilled from an oil-bath at 230—240°/15 mm., using a distillation flask with a wide side arm and short distillation path. The distillate solidified to an almost colourless solid which crystallised from light petroleum (b. p. 80—100°) as practically colourless needles of the *trichloro*-compound, m. p. 131° (Found: N, 12·0. $C_8H_3N_2Cl_3$ requires N, 12·0%).

4-Chloroanthranilic acid (V; R = OH, R′ = H, R″ = Cl).—4-Chloroacet-*o*-toluidide (183·5 g.), suspended in water (3 l.) containing anhydrous magnesium sulphate (360 g.), was stirred at 85—95° whilst potassium permanganate (360 g., 2·3 mols.) was added during 3 hours. Stirring was then continued for 2 hours, excess of sodium carbonate added, and manganese dioxide removed. The hot filtrate was acidified with hydrochloric acid and cooled, and the 4-chloro-2-acetamidobenzoic acid was collected and purified by dissolution in sodium carbonate and reprecipitation with acid (yield, 186 g.); m. p. 212°. This acetyl derivative (107 g.) was hydrolysed to 4-chloroanthranilic acid by warming it with hydrochloric acid (500 c.c.) until frothing moderated and then refluxing for 3 hours after the addition of a further quantity of hydrochloric acid (100 c.c.). The product was collected after cooling, washed well with water, and dried (yield, 71 g.); m. p. 224°.

7-Chloro-2 : 4-dihydroxyquinazoline (III; R = H, R′ = Cl).—In B.P. 315,451 it is mentioned that 7-chloro-2 : 4-dihydroxyquinazoline is prepared by heating 4-chloroanthranilic acid with urea or potassium cyanate, but the compound is not there characterised (cf. B.P. 288,159). 4-Chloroanthranilic acid (17·15 g.) was dissolved in water (180 c.c.) and sodium hydroxide (9·25 c.c. of 35%) at 40°, and sodium cyanate (7·2 g.) added with stirring. When the cyanate had dissolved, acetic acid (6 c.c.) was added, and stirring continued at room temperature for 6 hours. After being left overnight, the solution was filtered and the filtrate acidified with hydrochloric acid to give presumably 4-chloro-2-ureidobenzoic acid, m. p. 190° (yield, 8·7 g.). This compound (6·7 g.) was added to sodium hydroxide (10 c.c. of 30%). The mixture became very thick. It was extracted with boiling water (300 c.c.), and the sparingly soluble sodium salt (yield, 2·15 g.) filtered off. This gave 7-chloro-2 : 4-dihydroxyquinazoline, m. p. 347—348° (yield, 1·7 g.), on boiling with dilute hydrochloric acid. A further quantity of the same substance (2·83 g.), m. p. 346°, was obtained by acidifying the mother liquors from the isolation of the sodium salt with acetic acid.

2 : 4 : 7-Trichloroquinazoline (IV; R = H, R′ = Cl).—This was prepared by the method described above for the corresponding 2 : 4 : 6-trichloro-compound (method of B.PP. 288,159, 315,451; compound not characterised) and also by the following method. 7-Chloro-2 : 4-dihydroxyquinazoline (40 g.), phosphoryl chloride (150 c.c.), and dimethylaniline (15 c.c.) were refluxed for 5 hours. The cooled mixture was poured on ice, and the product extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue crystallised from light petroleum (b. p. 80—100°) to give 2 : 4 : 7-*trichloroquinazoline* as colourless needles, m. p. 127° (Found: N, 11·6. $C_8H_3N_2Cl_3$ requires N, 12·0%).

2 : 4-Dichloro-6-nitroquinazoline (IV; R = NO_2, R′ = H), prepared from 6-nitro-2 : 4-dihydroxyquinazoline (Bogert and Scatchard, *loc. cit.*) by the action of phosphoryl chloride and dimethylaniline as described for the preceding compound, crystallised from light petroleum (b. p. 80—100°) as pale yellow needles, m. p. 127—129° (Found: N, 17·3. $C_8H_3O_2N_3Cl_2$ requires N, 17·2%). This compound is mentioned but not characterised in B.PP. 287,179, 288,159. It is there stated to have been prepared by the action of phosphorus pentachloride–phosphoryl chloride on 6-nitro-2 : 4-dihydroxyquinazoline, and we have also used this method satisfactorily (procedure as for 2 : 4 : 6-trichloroquinazoline). The compound has b. p. 220—230°/16—20 mm.

4-Nitroanthranilic acid (V; R = OH, R′ = H, R″ = NO_2).—4-Nitroacet-*o*-toluidide (194 g.), water (4 l.), and magnesium sulphate (heptahydrate, 130 g.) were heated to 100° with stirring. Potassium permanganate (330 g.) was then added gradually during 2—3 hours with stirring (additions made as decolorisation occurred), the volume being kept constant by the addition of hot water. When all the permanganate had been added and decolorisation was complete, the mixture was filtered hot and the filter cake washed with hot water (700 c.c.). The filtrate and washings were combined and allowed to cool overnight. After filtration from unchanged material, acidification of the filtrate with hydrochloric

acid precipitated 4-nitro-2-acetamidobenzoic acid (yield, 145·5 g.). This was hydrolysed by boiling it with 5N-hydrochloric acid (1200 c.c.) for 1 hour with stirring. The clear solution was poured into water (3600 c.c.), and the precipitated 4-nitroanthranilic acid filtered off, washed, and dried (yield, 97 g.); m. p. 263—264°.

7-*Nitro*-2 : 4-*dihydroxyquinazoline* (III; R = H, R′ = NO_2).—(*a*) 4-Nitroanthranilic acid (18·2 g.), urea (50 g.), and water (50 c.c.) were stirred and boiled under reflux for 24 hours. The orange-coloured solution gradually deposited pale yellow crystals. These were filtered off hot, washed with boiling water, and extracted with boiling alcohol to leave 7-*nitro*-2 : 4-*dihydroxyquinazoline* (yield, 8 g.) as tan-coloured crystals, m. p. 338—339° (Found : N, 21·0. $C_8H_5O_4N_3$ requires N, 20·3%).

(*b*) 4-Nitroanthranilic acid (8·6 g.) was dissolved in hot water (250 c.c.) as the sodium salt, and the solution cooled to <30° and treated with potassium cyanate (10 g.) and 10N-hydrochloric acid (10 c.c.) with vigorous stirring. After 20 hours' stirring the resulting orange-yellow 4-nitro-2-ureidobenzoic acid was filtered off and crystallised from water; m. p. 224—225°. This compound (2·9 g.) when heated on the steam-bath for 2 hours with 10N-hydrochloric acid (10 c.c.) gave 7-nitro-2 : 4-dihydroxyquinazoline (isolated by dilution with water and filtration), m. p. 339°, identical with material made by method (*a*).

2 : 4-*Dichloro*-7-*nitroquinazoline* (IV; R = H, R′ = NO_2), prepared from the above compound by the action of phosphorus pentachloride–phosphoryl chloride and isolated by distillation of the reaction mixture from a bath at 250—270°/10 mm., formed a yellowish solid, m. p. 148—150° (Found : N, 17·4. $C_8H_3O_2N_3Cl_2$ requires N, 17·2%).

3-*Ureido*-p-*tolunitrile*.—3-Amino-*p*-tolunitrile (4·75 g.) (von Niementowski, *loc. cit.*) in acetic acid (20 c.c.) and water (5 c.c.) was treated with powdered sodium cyanate (2·1 g.) suspended in water (10 c.c.), and the mixture stirred for 4 hours and then left overnight. The crystalline product was filtered off, washed well with water, and crystallised from dilute alcohol. The *compound*, which sublimed readily when heated, formed yellowish needles, m. p. 225° (sealed tube) (Found : C, 60·5; H, 5·5; N, 23·3. $C_9H_9ON_3$, $0·25H_2O$ requires C, 60·1; H, 5·3; N, 23·4%).

2 : 4-*Dihydroxy*-7-*methylquinazoline* (III; R = H, R′ = Me).—(*a*) A solution of 4-methylanthranilic acid (15·1 g.) in hot water (20 c.c.) and hydrochloric acid (9 c.c.) was diluted to 200 c.c. with cold water and a suspension of sodium cyanate (8·4 g.) in water (30 c.c.) added. After stirring, the precipitated product, m. p. 187° (decomp.), presumably 3-ureido-*p*-toluic acid (VI; R = OH, R′ = H, R″ = Me), was filtered off, washed with water, and dried (yield, 8·1 g.). This was heated on the steam-bath for 1 hour with hydrochloric acid (15 c.c.) and water (4 c.c.), the mixture cooled and filtered, and the 2 : 4-dihydroxy-7-methylquinazoline collected. After purification *via* its sodium salt it had m. p. 320° (von Niementowski, *loc. cit.*, gives m. p. 317°).

(*b*) 4-Methylanthranilamide (13 g.) in acetic acid (80 c.c.) and water (20 c.c.) was treated with a suspension of sodium cyanate (8·4 g.) in water (40 c.c.) with stirring. In a short time the mixture set to a mass of crystals. After 2 hours these were filtered off, washed with water, and dried. This 3-ureido-*p*-toluamide, m. p. 188° (decomp.) [mixed m. p. with above 3-ureido-*p*-toluic acid, 174° (decomp.)] (yield, 16·6 g.), was not analysed but converted directly into 2 : 4-dihydroxy-7-methylquinazoline, m. p. and mixed m. p. 320°, by heating it on the steam-bath for 1 hour with hydrochloric acid (30 c.c.) and water (8 c.c.).

(*c*) 3-Ureido-*p*-tolunitrile (1·25 g.) and sodium hydroxide solution (20 c.c. of 35%) were refluxed for 20 minutes. The solid which had separated was filtered off when cold, dissolved in hot water, and the solution acidified with acetic acid to give 2 : 4-dihydroxy-7-methylquinazoline as colourless needles, m. p. and mixed m. p. 320° (yield, 0·52 g.).

3-Ureido-*p*-tolunitrile was also converted into (III; R = H, R′ = Me) by refluxing it (1·25 g.) with hydrochloric acid (20 c.c.) for 1 hour.

By treatment with phosphorus pentachloride–phosphoryl chloride, 2 : 4-dihydroxy-7-methylquinazoline was converted into 2 : 4-dichloro-7-methylquinazoline which distilled at 220—250° (bath temp.)/15—20 mm. and had m. p. 113° (cf. B.P. 288,159).

2-*Amino*-6-*methoxybenzamide* (VIII).—2-Nitro-6-methoxybenzonitrile (VII) (4·45 g.) (Lobry de Bruyn, *loc. cit.*) in methanol (100 c.c.) was reduced with hydrogen–Raney nickel at 20° and atmospheric pressure. On evaporation of the filtered, carbon-treated solution, 2-amino-6-methoxybenzamide crystallised in needles (yield, 2·3 g.), m. p. 149—150° undepressed by an authentic sample prepared by hydrolysis of 2-amino-6-methoxybenzonitrile (cf. Friedländer *et al.*, *loc. cit.*).

2-*Ureido*-6-*methoxybenzamide* (IX).—(*a*) 2-Amino-6-methoxybenzonitrile (X) (26·8 g.) (Lobry de Bruyn, *loc. cit.*) in acetic acid (175 c.c.) was stirred for 4 hours with finely powdered sodium cyanate (17·5 g.). After standing overnight the crystalline *product* was collected and washed with water (yield, 24 g.); m. p. 178—180° (decomp.). By crystallisation from water it was obtained as a cream-coloured solid, m. p. 198° (decomp.) (Found : N, 20·1. $C_9H_{11}O_3N_3$ requires N, 20·1%).

(*b*) 2-Amino-6-methoxybenzamide (VIII) (6·2 g.) in acetic acid (40 c.c.) was stirred with sodium cyanate (5 g.) suspended in water (20 c.c.) overnight. Next day the mixture was diluted with water (60 c.c.), and the product filtered off and washed with water (yield, 5·7 g.). It was shown to be identical (m. p. and mixed m. p.) with 2-ureido-6-methoxybenzamide made by method (*a*).

2 : 4-*Dihydroxy*-5-*methoxyquinazoline* (XI; R = R′ = OH).—The preceding compound (2·75 g.) was boiled with sodium hydroxide (10 c.c. of 35%). After 20 minutes the mixture was cooled, and the resulting sodium salt filtered off, dissolved in water (100 c.c.), treated with carbon, and precipitated with acetic acid. The *product* (2·4 g.) crystallised from aqueous alcohol; m. p. 308° (Found : N, 13·9, 13·9. $C_9H_8O_3N_2$, $0·5H_2O$ requires N, 13·9%). Treatment of this compound with phosphoryl chloride and dimethylaniline, in the manner described above for 2 : 4 : 7-trichloroquinazoline, gave 2 : 4-dichloro-5-methoxyquinazoline (XI; R = R′ = Cl) as colourless needles, m. p. 160—162°.

2 : 4-*Dichloro*-6-*methoxyquinazoline* (IV; R = OMe, R′ = H).—2-Nitro-5-methoxybenzoic acid (20 g.) (Part XVI, *loc. cit.*) was reduced catalytically using Raney nickel in methanol, and the crude 5-methoxyanthranilic acid obtained by filtration and evaporation of the methanol was dissolved in 2N-hydrochloric acid (60 c.c.) and stirred overnight with sodium cyanate (8·5 g.). The precipitated

2-ureido-5-methoxybenzoic acid [m. p. 186° (decomp.)] was filtered off, washed with water, and heated on the steam-bath with excess of hydrochloric acid for 1 hour to give 2 : 4-dihydroxy-6-methoxyquinazoline (not analysed), m. p. 316—318° (yield, 5 g.). This compound (7·5 g.) was heated under reflux with phosphorus pentachloride (16·3 g.) and phosphoryl chloride (10 c.c.) for 3 hours, the phosphoryl chloride removed under reduced pressure, and the residue distilled from a bath at 250—300°/15 mm. to give 2 : 4-*dichloro*-6-*methoxyquinazoline* as a yellowish crystalline solid, m. p. 171° (Found: Cl, 31·0. $C_9H_6ON_2Cl_2$ requires Cl, 31·0%).

4-*Methoxyanthranilamide* (V; R = NH_2, R′ = H, R″ = OMe).—Iron pin dust (80 g.), alcohol (400 c.c.), and hydrochloric acid (10 c.c.) were stirred and boiled under reflux for 10 minutes. 2-Nitro-4-methoxybenzonitrile (45 g.) (Cook, Heilbron, Reed, and Strachan, *J.*, 1945, 861) was added during 15 minutes, and the mixture then refluxed with stirring overnight. Sodium carbonate was added to precipitate dissolved iron, and the mixture was filtered hot, the residue being washed with a little boiling alcohol. The filtrate was concentrated to 100 c.c. On cooling, 4-methoxyanthranilamide was deposited (yield, 18·5 g.). It crystallised from alcohol in plates, m. p. 153° (Chapman, Gibson, and Mann, Part XVI, *loc. cit.*, give m. p. 155—155·5°) (Found: N, 16·7. Calc. for $C_8H_{10}O_2N_2$: N, 16·9%). Dilution of the alcoholic mother liquors from the 4-methoxyanthranilamide with water gave 2-amino-4-methoxybenzonitrile (yield, 12·4 g.) which crystallised from aqueous alcohol in colourless needles, m. p. 92° (Cook *et al.*, *loc. cit.*, give m. p. 96°) (Found: N, 19·3. Calc. for $C_8H_8ON_2$: N, 19·0%). The nitrile was converted into the amide by treatment with hydrogen peroxide in aqueous alcoholic sodium hydroxide, but in poor yield.

2-*Ureido*-4-*methoxybenzamide* (VI; R = NH_2, R′ = H, R″ = OMe).—4-Methoxyanthranilamide (18·5 g.) in acetic acid (100 c.c.) was treated with a suspension of sodium cyanate (11 g.) in water (50 c.c.) and stirred well. After 1 hour the 2-*ureido*-4-*methoxybenzamide* was collected, washed, and crystallised from water; colourless rhombic plates (yield, 21·75 g.), m. p. 208° (decomp.) (Found: N, 19·8. $C_9H_{11}O_3N_3$ requires N, 20·1%).

2 : 4-*Dihydroxy*-7-*methoxyquinazoline* (III; R = H, R′ = OMe).—2-Ureido-4-methoxybenzamide (21·5 g.) was heated with 8N-hydrochloric acid (45 c.c.) on the steam-bath for 1 hour. The resulting product was collected and stirred with 35% sodium hydroxide (50 c.c.) to form the sodium salt. This was filtered off and dissolved in hot water (500 c.c.), and the clarified solution precipitated with acetic acid to give 2 : 4-dihydroxy-7-methoxyquinazoline (yield, 11·2 g.) which crystallised from alcohol in colourless prisms, m. p. 300—301° (Found: C, 56·2; H, 4·2; N, 14·9. Calc. for $C_9H_8O_3N_2$: C, 56·2; H, 4·2; N, 14·6%) (Chapman, Gibson, and Mann, *loc. cit.*, give m. p. 299—301°).

2 : 4-*Dichloro*-7-*methoxyquinazoline* (IV; R = H, R′ = OMe).—The above 2 : 4-dihydroxy-7-methoxyquinazoline was converted into 2 : 4-dichloro-7-methoxyquinazoline by treatment with phosphorus pentachloride and phosphoryl chloride as described by Chapman *et al.* (*loc. cit.*). Instead of extracting the product with light petroleum we preferred isolation by distillation from a bath at 260—290°/15 mm. It crystallised from light petroleum (b. p. 100—120°) as practically colourless needles, m. p. 120—121° (lit. 121—121·5°) (Found: N, 12·3; Cl, 30·7. Calc. for $C_9H_6ON_2Cl_2$: N, 12·2; Cl, 31·0%).

2 : 4-*Dihydroxy*-8-*methoxyquinazoline* (XII; R = R′ = OH).—(*a*) 2-Nitro-3-methoxybenzoic acid (30·3 g.) (Hodgson and Beard, *J.*, 1926, 154) was refluxed with thionyl chloride (30 c.c.) for 1 hour, and the excess of the latter then removed under diminished pressure. The crystalline residue was cooled and treated with methanol (100 c.c.) under reflux, and the vigorous reaction was completed by subsequent boiling for 5 minutes. On cooling, methyl 2-nitro-3-methoxybenzoate (colourless plates, m. p. 140°, from methanol) separated (yield, 27·4 g.). Catalytic hydrogenation with Raney nickel in methanol afforded methyl 3-methoxyanthranilate (colourless thick elongated prisms, m. p. 45°, from methanol). (*b*) Methyl 3-methoxyanthranilate (12·5 g.) in acetic acid (30 c.c.) was treated with sodium cyanate (7 g.) suspended in water (15 c.c.) with stirring, and the mixture left for 48 hours. Water (50 c.c.) was added, and the crystalline product (methyl 2-ureido-3-methoxybenzoate, m. p. 148—150°) collected (yield, 10·55 g.) and boiled with water (100 c.c.) for 1 hour. The resulting 2 : 4-dihydroxy-8-methoxyquinazoline, collected hot, had m. p. 258—259° unchanged by purification by dissolution in sodium hydroxide solution and reprecipitation with acid (Found: C, 56·5; H, 4·2; N, 14·8. Calc. for $C_9H_8O_3N_2$: C, 56·2; H, 4·2; N, 14·6%).

2 : 4-*Dichloro*-8-*methoxyquinazoline* (XII; R = R′ = Cl).—Prepared from 2 : 4-dihydroxy-8-methoxyquinazoline, phosphorus pentachloride, and phosphoryl chloride, this *compound* distilled from a bath at 230—260°/20 mm. and formed a pale yellow solid, m. p. 154—156° (Found: Cl, 30·3. $C_9H_6ON_2Cl_2$ requires Cl, 31·0%).

2-*Ureido*-4 : 5-*dimethoxybenzoic acid* (VI; R = H, R′ = R″ = OMe).—6-Nitroveratric acid (45 g.) in methanol (300 c.c.) was reduced catalytically over Raney nickel, ammonia being added during the reduction to bring the acid into solution. When hydrogen absorption was complete the suspension was treated with sodium hydroxide, and, after removal of the methanol by steam distillation, the volume was reduced to 400 c.c. under reduced pressure. No product separated on neutralisation or faint acidification with acetic acid (Tiemann and Matsmoto, *Ber.*, 1876, **9**, 942, stated that free 6-aminoveratric acid could not be isolated, whereas Heidelberger and Jacobs, *J. Amer. Chem. Soc.*, 1919, **41**, 2142, described it as sparingly soluble in water), but a small portion of the solution treated with acetic anhydride gave 6-acetamidoveratric acid, m. p. 226° (Simonsen and Race, *J.*, 1918, **113**, 26, give m. p. 228°). The bulk of the solution, treated with sodium cyanate (15 g.) and acetic acid (15 c.c.), gave 2-*ureido*-4 : 5-*dimethoxybenzoic acid* (yield, 34·5 g.), m. p. 162—163° (decomp.) (Found: N, 10·6. $C_{10}H_{12}O_5N_2,H_2O$ requires N, 10·9%).

2 : 4-*Dihydroxy*-6 : 7-*dimethoxyquinazoline* (III; R = R′ = OMe).—The above 2-ureido-4 : 5-dimethoxybenzoic acid (38·5 g.) was stirred for 1 hour with sodium hydroxide (50 c.c. of 35%). The precipitated sodium salt was filtered off, dissolved in boiling water (500 c.c.), and the filtered solution poured into acetic acid (50 c.c.). The precipitated *product* was filtered off and dried (yield, 10·1 g.). It formed cream-coloured platelets, m. p. 323—325° (Found: N, 11·9. $C_{10}H_{10}O_4N_2,H_2O$ requires N, 11·7%). A further quantity was obtained by treating the original mother liquors from the sodium

salt with sodium cyanate (25 g.) and acidification with acetic acid followed by cyclisation of the resulting 2-ureido-4 : 5-dimethoxybenzoic acid by heating at 95—100° with hydrochloric acid (30 c.c.) and water (10 c.c.).

2 : 4-*Dichloro*-6 : 7-*dimethoxyquinazoline* (IV; R = R′ = OMe).—2 : 4-Dihydroxy-6 : 7-dimethoxyquinazoline (16 g.), phosphoryl chloride (45 c.c.), and dimethylaniline (4·5 c.c.) were refluxed for 4·5 hours, the reaction mixture poured on ice, and the product extracted with ether. Evaporation of the dried ether solution gave the *product* which crystallised from light petroleum (b. p. 80—100°) as colourless needles, m. p. 158° (Found : N, 10·8. $C_{10}H_8O_2N_2Cl_2$ requires N, 10·8%).

2 : 4-*Dihydroxy*-6 : 7-*benzoquinazoline* (III; RR′ = benzo).—2-Naphthylamine-3-carboxylic acid (30 g.), urea (60 g.), and phenol (150 g.) were fused together and the mixture stirred under reflux for ½ hour. The resulting melt was cooled to 100°, and alcohol (150 c.c.) added cautiously. The mixture was stirred until cold, and the colourless crystalline *product* then filtered off, washed with alcohol, and dried (yield, 31 g.); m. p. 356° raised to 358—359° by recrystallisation from phenol (Found : C, 67·3; H, 4·0; N, 13·2. $C_{12}H_8O_2N_2$ requires C, 67·8; H, 3·8; N, 13·2%). We are indebted to Dr. F. H. Slinger for this preparation.

2 : 4-*Dichloro*-6 : 7-*benzoquinazoline* (IV; R and R′ = benzo), prepared from the preceding compound by the action of phosphorus pentachloride and phosphoryl chloride and purified by distillation from a bath at 270—300°/10—15 mm., formed an orange-coloured solid, m. p. 184° (Found : N, 11·0. $C_{12}H_6N_2Cl_2$ requires N, 11·25%).

2 : 6-*Dichloro*-4-*β*-*diethylaminoethylaminoquinazoline* (II; R = R″ = R‴ = H, R′ = Cl).—Finely ground 2 : 4 : 6-trichloroquinazoline (9·6 g.), water (75 c.c.), and *β*-diethylaminoethylamine (5 g.) were stirred together at room temperature. After 1 hour, and subsequently at intervals, sodium hydroxide solution was added so as to maintain the alkalinity to Clayton-yellow. When the alkalinity no longer decreased, the mixture was stirred overnight and then acidified with hydrochloric acid. Unreacted 2 : 4 : 6-trichloroquinazoline was filtered off and washed with water. The filtrate was basified with ammonia, and the precipitated product (gummy) washed with water by decantation and triturated with ether; it then solidified. Crystallised from light petroleum (b. p. 100—120°), 2 : 6-*dichloro*-4-*β*-*diethylaminoethylaminoquinazoline* formed colourless crystals, m. p. 135—136° (Found : N, 17·9. $C_{14}H_{18}N_4Cl_2$ requires N, 17·9%).

Using the same method, the following 2-chloro-4-*β*-diethylaminoethylaminoquinazolines carrying different substituents were made by condensation of *β*-diethylaminoethylamine with the appropriate substituted 2 : 4-dichloroquinazoline. 2 : 7-*Dichloro*-4-*β*-*diethylaminoethylaminoquinazoline* (II; R = R′ = R‴ = H, R″ = Cl) was precipitated initially as a *dihydrate*, m. p. 84—85° (Found: Cl, 20·7; $C_{14}H_{18}N_4Cl_2,2H_2O$ requires Cl, 20·35%); the anhydrous compound crystallised from light petroleum (b. p. 80—100°) as faintly yellowish laminæ, m. p. 119° (Found : C, 53·6; H, 5·6; N, 17·6. $C_{14}H_{18}N_4Cl_2$ requires C, 53·6; H, 5·75; N, 17·9%). 2-*Chloro*-6-*nitro*-4-*β*-*diethylaminoethylaminoquinazoline* (II; R = R″ = R‴ = H, R′ = NO_2) formed yellow needles from light petroleum (b. p. 80—100°), m. p. 125—126° (Found : N, 21·9. $C_{14}H_{18}O_2N_5Cl$ requires N, 21·65%). 2-*Chloro*-7-*nitro*-4-*β*-*diethylaminoethylaminoquinazoline* (II; R = R′ = R‴ = H, R″ = NO_2) crystallised from light petroleum (b. p. 80—100°) as yellow laminæ, m. p. 117° (Found : N, 22·0. $C_{14}H_{18}O_2N_5Cl$ requires N, 21·65%). 2-*Chloro*-4-*β*-*diethylaminoethylamino*-7-*methylquinazoline* (II; R = R′ = R‴ = H, R″ = Me) separated from light petroleum (b. p. 80—100°) as colourless needles, m. p. 112° (Found : N, 19·3; Cl, 12·2. $C_{15}H_{21}N_4Cl$ requires N, 19·1; Cl, 12·1%). 2-*Chloro*-4-*β*-*diethylaminoethylamino*-5-*methoxyquinazoline* (II; R = OMe, R′ = R″ = R‴ = H) formed a trihydrate, m. p. 100—102° (Found : N, 15·7. $C_{15}H_{21}ON_4Cl,3H_2O$ requires N, 15·45%). 2-*Chloro*-4-*β*-*diethylaminoethylamino*-6-*methoxyquinazoline* (II; R = R″ = R‴ = H, R′ = OMe) was isolated as a hydrate, m. p. 65—66° (Found : N, 14·9. $C_{15}H_{21}ON_4Cl,4H_2O$ requires N, 14·7%). 2-Chloro-4-*β*-diethylaminoethylamino-7-methoxyquinazoline (II; R = R′ = R‴ = H, R″ = OMe) crystallised from light petroleum (b. p. 80—100°) as colourless needles, m. p. 110—111° (Found : C, 58·0; H, 6·9; N, 17·8. Calc. for $C_{15}H_{21}ON_4Cl$: C, 58·3; H, 6·8, N, 18·15%) (Chapman, Gibson, and Mann, *loc. cit.*, give m. p. 108—109°). 2-*Chloro*-4-*β*-*diethylaminoethylamino*-8-*methoxyquinazoline* (II; R = R′ = R″ = H, R‴ = OMe) formed a colourless crystalline solid, m. p. 134—135° (Found : N, 18·1. $C_{15}H_{21}ON_4Cl$ requires N, 18·15%). 2-*Chloro*-4-*β*-*diethylaminoethylamino*-6 : 7-*dimethoxyquinazoline* (II; R = R‴ = H, R′ = R″ = OMe) had m. p. 116—117° (Found : N, 14·6. $C_{16}H_{23}O_2N_4Cl,2H_2O$ requires N, 14·95%). 2-*Chloro*-4-*β*-*diethylaminoethylamino*-6 : 7-*benzoquinazoline* (II; R = R‴ = H, R′R″ = benzo) crystallised from light petroleum as pale yellow needles, m. p. 140—142° (Found : N, 15·8. $C_{18}H_{21}N_4Cl,H_2O$ requires N, 16·15%).

6-*Chloro*-2-p-*chloroanilino*-4-*β*-*diethylaminoethylaminoquinazoline* (I; R = R″ = R‴ = H, R′ = Cl).—2 : 6-Dichloro-4-*β*-diethylaminoethylaminoquinazoline (6·3 g.), *p*-chloroaniline (5·1 g.), and acetic acid (10 c.c.) were refluxed for 2 hours, and the solution then cooled and diluted with water (100 c.c.). After being filtered from acet-*p*-chloroanilide, the solution was made alkaline with sodium carbonate and steam distilled to remove unchanged *p*-chloroaniline. The residual oily base was washed with water by decantation and dissolved in 10% acetic acid (50 c.c.), the solution was treated with carbon and filtered, and hydrochloric acid (10 c.c.) was added. The precipitated *dihydrochloride* (4258) crystallised from water as colourless needles, m. p. 282° (Found : C, 47·3; H, 5·8; N, 13·5. $C_{20}H_{23}N_5Cl_2,2HCl,1·5H_2O$ requires C, 47·6; H, 5·6; N, 13·9%).

A similar method was used for the preparation of the following compounds of the same type. 7-Chloro-2-*p*-chloroanilino-4-*β*-diethylaminoethylaminoquinazoline (I; R = R′ = R‴ = H, R″ = Cl) crystallised from light petroleum (b. p. 80—100°) as yellowish nodular crystals, m. p. 121—122°, and gave a *dihydrochloride* (3918) which separated from water as small colourless needles, m. p. 280—283° (Found : C, 50·0; H, 5·4; N, 14·4. $C_{20}H_{23}N_5Cl_2,2HCl$ requires C, 50·3; H, 5·25; N, 14·7%). 6-*Nitro*-2-p-*chloroanilino*-4-*β*-*diethylaminoethylaminoquinazoline* (I; R = R″ = R‴ = H, R′ = NO_2) crystallised from alcohol as orange yellow needles, m. p. 200—201° (Found : C, 57·7; H, 5·2; N, 20·2. $C_{20}H_{23}O_2N_6Cl$ requires C, 57·9; H, 5·55; N, 20·3%), and its *dihydrochloride* (4537) from water as yellowish needles, m. p. 266° (Found : Cl′, 13·8. $C_{20}H_{23}O_2N_6Cl,2HCl,1·5H_2O$ requires Cl′, 13·8%). 7-*Nitro*-2-p-*chloro*-

anilino-4-β-diethylaminoethylaminoquinazoline (I; R = R′ = R‴ = H, R″ = NO_2) (4259) (dihydrochloride, m. p. 246°) crystallised from alcohol as reddish-orange laminæ, m. p. 159·5—160° (Found: C, 57·9; H, 5·5; N, 20·0. $C_{20}H_{23}O_2N_6Cl$ requires C, 57·9; H, 5·55; N, 20·3%). 2-p-*Chloroanilino-4-β-diethylaminoethylamino-7-methylquinazoline dihydrochloride* (as I; R = R′ = R‴ = H, R″ = Me) (3931) crystallised from dilute hydrochloric acid as colourless needles, m. p. 264° (Found: C, 54·8; H, 6·1; N, 15·7. $C_{21}H_{26}N_5Cl,2HCl$ requires C, 55·2; H, 6·1; N, 15·35%). 2-*p*-Chloroanilino-4-β-diethylaminoethylamino-6-methoxyquinazoline (I; R = R″ = R‴ = H, R′ = OMe) formed a *dihydrochloride* (4624) which separated from water as short colourless prisms, m. p. 248—249° (Found: C, 49·3; H, 6·3. $C_{21}H_{26}ON_5Cl,2HCl,2H_2O$ requires C, 49·6; H, 6·3%). 2-*p*-Chloroanilino-4-β-diethylaminoethylamino-7-methoxyquinazoline (I; R = R′ = R‴ = H, R″ = OMe) afforded a *dihydrochloride* (3963) which crystallised from water as colourless prisms, m. p. 230—232° (Found: C, 50·4; H, 6·5; N, 14·1. $C_{21}H_{26}ON_5Cl,2HCl,1·5H_2O$ requires C, 50·4; H, 6·2; N, 14·05%), and the corresponding 8-methoxy-compound (I; R = R′ = R″ = H, R‴ = OMe) was isolated as its *dihydrochloride* (4609) which separated from water as colourless prisms, m. p. 274—275° (Found: C, 51·6; H, 6·3; N, 13·8; Cl′, 14·4. $C_{21}H_{26}ON_5Cl,2HCl,H_2O$ requires C, 51·3; H, 6·1; N, 14·3; Cl′, 14·5%). 2-*p*-Chloroanilino-4-β-diethylaminoethylamino-6:7-dimethoxyquinazoline (I; R = R‴ = H, R′ = R″ = OMe) gave a *dihydrochloride* (4185) which crystallised from water as colourless laminæ, m. p. 255—256° (Found: C, 51·4; H, 6·1; N, 13·2. $C_{22}H_{28}O_2N_5Cl,2HCl,0·5H_2O$ requires C, 51·6; H, 6·05; N, 13·7%). 2-*p*-Chloroanilino-4-β-diethylaminoethylamino-6:7-benzoquinazoline (I; R = R‴ = H, R′ and R″ = benzo) formed a *dihydrochloride* (3964) which was precipitated from a hot aqueous solution by the addition of hydrochloric acid as small sulphur-yellow prisms, m. p. 286—287° (Found: C, 53·2; H, 6·2; N, 12·5. $C_{24}H_{26}N_5Cl,2HCl,3H_2O$ requires C, 52·7; H, 6·2; N, 12·8%).

2-p-*Chloroanilino-4-β-diethylaminoethylamino-5-methoxyquinazoline* (I; R′ = R″ = R‴ = H, R = OMe).—2-Chloro-4-β-diethylaminoethylamino-5-methoxyquinazoline (3 g.), *p*-chloroaniline hydrochloride (3·3 g.), water (20 c.c.), and 10N-hydrochloric acid (0·1 c.c.) were boiled for 1 hour, the resulting solution treated with carbon and filtered, and a few drops of hydrochloric acid added. The product separated slowly on cooling as the *dihydrochloride* (5124) which was recrystallised from very dilute hydrochloric acid; colourless micro-needles, m. p. 187—189° (Found: C, 49·3; H, 6·2; N, 13·8. $C_{21}H_{26}ON_5Cl,2HCl,2H_2O$ requires C, 49·6; H, 6·3; N, 13·8%).

6-*Amino*-2-p-*chloroanilino*-4-β-*diethylaminoethylaminoquinazoline* (I; R = R″ = R‴ = H, R′ = NH_2).—6-Nitro-2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline (6·5 g.) suspended in methanol (150 c.c.) was reduced catalytically over Raney nickel at room temperature and pressure. When the theoretical hydrogen-absorption had taken place, the solution was filtered from catalyst and evaporated to dryness. The residue was dissolved in 5% acetic acid (40 c.c.) (charcoal) and filtered, and hydrochloric acid (10 c.c.) added. The *trihydrochloride* (4544) which separated slowly was collected and recrystallised from water, forming practically colourless needles, m. p. 180° resolidifying and remelting at 286° (Found: C, 41·1; H, 6·5; N, 14·3; Cl′, 17·6. $C_{20}H_{25}N_6Cl,3HCl,5H_2O$ requires C, 41·2; H, 6·5; N, 14·4; Cl′, 18·25%).

7-*Amino*-2-p-*chloroanilino*-4-β-*diethylaminoethylaminoquinazoline* (I; R = R′ = R‴ = H, R″ = NH_2).—Prepared similarly by catalytic reduction of 7-nitro-2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline, this formed a *dihydrochloride* (4213) which separated from water in colourless hair-fine needles, m. p. 295—296° (Found: C, 49·8; H, 6·3; N, 17·6; Cl′, 15·1. $C_{20}H_{25}N_6Cl,2HCl,1·5H_2O$ requires C, 49·55; H, 6·2; N, 17·4; Cl′, 14·7%).

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357. *Synthetic Antimalarials. Part XXXII. Some 4-Arylamino- and 4-Arylthio-2-aminoalkylaminoquinazolines, and 2-Arylthio-4-aminoalkylaminoquinazolines.*

By F. H. S. CURD, E. HOGGARTH, J. K. LANDQUIST, and F. L. ROSE.

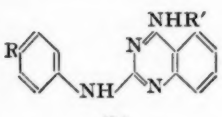
The investigation of quinazoline derivatives for antimalarial activity described in some of the earlier papers of this series (*J.*, 1947, 775, 890, and preceding paper) has been extended by the preparation of some 4-arylamino-2-aminoalkylaminoquinazolines and of some related derivatives carrying arylthio- and dialkylaminoalkylamino-groups in either the 2:4- or the 4:2- positions. None of these types exhibited any activity, and this is discussed in relation to the activity of the 2-arylamino-4-aminoalkylaminoquinazolines described in Part XIV and of the corresponding pyrimidine types.

In applying to the present quinazoline types the methods of synthesis earlier worked out for the analogous pyrimidine derivatives certain displacements of 4-arylamino- and arylthio-groups have been observed.

FROM previous investigations (Part XIV, Curd, Landquist, and Rose, *J.*, 1947, 775; Part XVI, Chapman, Gibson, and Mann, *ibid.*, p. 890; preceding paper) it was impossible to decide with any certainty whether the antimalarial activity of the 2-arylamino-4-aminoalkylaminoquinazolines of type (I; R′ = aminoalkyl) described in Part XIV originated from the same cause as that of the analogous 2-arylamino-4-aminoalkylamino-6-methylpyrimidines (III; X = NH, R′ = aminoalkyl). Had this indeed been the case, then it seemed reasonable to

expect that the isomeric 4-arylamino-2-aminoalkylaminoquinazolines (II; R′ = aminoalkyl), similarly related to the active 4-arylamino-2-aminoalkylamino-6-methylpyrimidines (IV; X = NH) described in Parts VI and IX (*J.*, **1946**, 370, 720), would also show activity. Several quinazolines of type (II) have therefore been prepared, but antimalarial tests against *P. gallinaceum* in chicks conducted on these compounds by Dr. D. G. Davey failed to disclose any activity. This would seem to indicate a different mode of action for the quinazolines of type (I) as compared with the pyrimidines of type (III; X = NH), despite the obvious structural resemblance of the two types, and it is not without interest to discuss these results in the light of the hypothesis advanced in an earlier communication (Part XII, *J.*, **1947**, 154) which sought to show that in certain antimalarial compounds positive activity was to be associated with the possibility of conjugation of a terminal alkylamino- or aminoalkylamino-group and an anilino-residue through a system made up of alternate carbon and nitrogen atoms. Such an arrangement would be provided in the case of the quinazolines by the polarised forms (or the tautomers corresponding thereto) represented by (I*a*) and (II*a*). If the conjugation hypothesis is applicable in the present instances then it must be that in type (I) the form (I*a*) provides a major contribution to a resonance hybrid whereas (II*a*) is insignificant with respect to type (II).

Alternatively, the biological results with type (II) may be compared with those yielded by the isosteric 4-arylamino-2-aminoalkylaminoquinolines (Part XVI, Curd, Raison, and Rose, *J.*, **1947**, 899) which exhibit but feeble activity. In this respect then the quinazoline system may be regarded from the biological standpoint as a quinoline derivative, and further evidence in support of this view is provided by the considerable antimalarial activities found in the 4-dialkylaminoalkylaminoquinazolines described in Part XVI (*loc. cit.*) and the corresponding substituted quinolines (see D.R.-P. 683,692), activities which are enhanced in both instances by the introduction of chlorine into the 7-position.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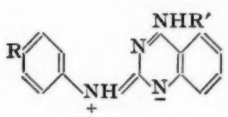
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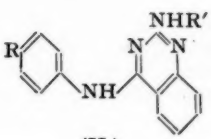
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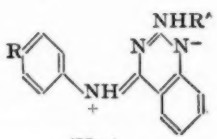
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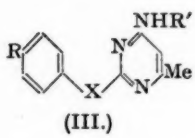
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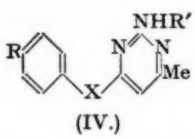
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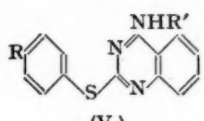
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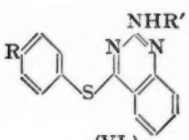
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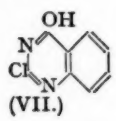
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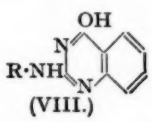
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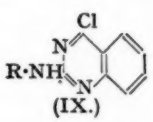
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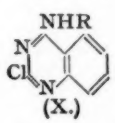
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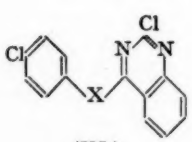
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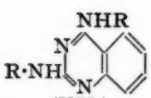
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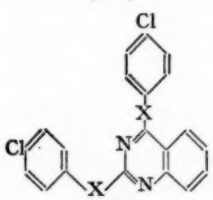
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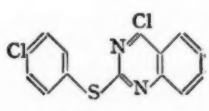

(XIV.)

A number of 4-dialkylaminoalkylamino-2-arylthio- and 2-dialkylaminoalkylamino-4-arylthio-quinazolines of types (V) and (VI) have also been prepared, but these showed no activity when tested against *P. gallinaceum* in chicks. The inactivity of the latter type is not very surprising in view of the inactivity of the analogous arylamino-type (II), but the former might have been expected to show some activity since it is related to the active quinazolines of type (I) in the same way that the dialkylaminoalkylamino-arylthiopyrimidines of types (III and IV; X = S) described in Part XV (Curd, Davis, Hoggarth, and Rose, *J.*, **1947**, 783) are related to the corresponding anilino-types (III and IV; X = NH).

Compounds of type (II) were prepared from 2-chloro-4-hydroxyquinazoline (VII). This, by

reaction with aminoalkylamines, gave 2-aminoalkylamino-4-hydroxyquinazolines (VIII), and these were converted by treatment with phosphoryl chloride into 4-chloro-2-aminoalkylaminoquinazolines (IX) which reacted with arylamines to give the desired 4-arylamino-2-aminoalkylaminoquinazolines. In this way the following quinazolines of type (II) were prepared: 4-*p*-chloroanilino-2-β-diethylaminoethylamino- (II; R = Cl, R′ = $[CH_2]_2$·NEt_2) (characterised as its *dihydrochloride* and *dipicrate*), 4-p-*chloroanilino*-2-*γ*-*diethylaminopropylamino*- (II; R = Cl, R′ = $[CH_2]_3$·NEt_2), the corresponding *p*-methoxyanilino-derivative (II; R = OMe, R′ = $[CH_2]_3$·NEt_2) (isolated as its *dihydrochloride*), 4-p-*chloroanilino*-2-*γ*-*piperidinopropylamino*- (II; R = Cl, R′ = $[CH_2]_3$·N$<[CH_2]_4>CH_2$) and 4-*p*-chloroanilino-2-*γ*-di-*n*-butylaminopropylamino- (II; R = Cl, R′ = $[CH_2]_3$·NBu^n_2) as its *dihydrochloride*. The 4-chloro-2-aminoalkylaminoquinazolines of type (IX) served also as intermediates for the preparation of two representatives of type (VI), *viz.*, 2-β-*diethylaminoethylamino*-4-p-*chlorophenylthioquinazoline* (R = Cl, R′ = $[CH_2]_2$·NEt_2) and 2-*γ*-*diethylaminopropylamino*-4-p-*chlorophenylthioquinazoline* (R = Cl, R′ = $[CH_2]_3$·NEt_2).

The 4-aminoalkylamino-2-arylthioquinazolines of type (V) were prepared by a route analogous to that first worked out for the corresponding arylamino-compounds (I) and described in Part XIV (*loc. cit.*), namely, by condensation of a 2-chloro-4-aminoalkylaminoquinazoline with a thiophenol. Thus, 2-chloro-4-*γ*-diethylaminopropylaminoquinazoline (X; R = $[CH_2]_3$·NEt_2) when fused with *p*-chlorothiophenol and thio-*p*-cresol respectively gave 4-*γ*-*diethylaminopropylamino*-2-p-*chlorophenylthio*- (V; R = Cl, R′ = $[CH_2]_3$·NEt_2) and 4-*γ*-*diethylaminopropylamino*-2-p-*tolylthioquinazoline* (V; R = Me, R′ = $[CH_2]_3$·NEt_2) while 2-chloro-4-β-diethylaminoethylaminoquinazoline (X; R = $[CH_2]_2$·NEt_2) and *p*-chlorothiophenol gave 4-β-*diethylaminoethylamino*-2-p-*chlorophenylthioquinazoline* (V; R = Cl, R′ = $[CH_2]_2$·NEt_2).

When attempts were made to prepare the above 4-*p*-chloroanilino-2-aminoalkylaminoquinazolines (II) and the corresponding 4-*p*-chlorophenylthio-compounds (VI) by alternative methods from (XI; X = NH) and (XI; X = S) respectively, certain displacements of the substituents in the 4-position of the quinazoline nucleus were observed in a number of cases.

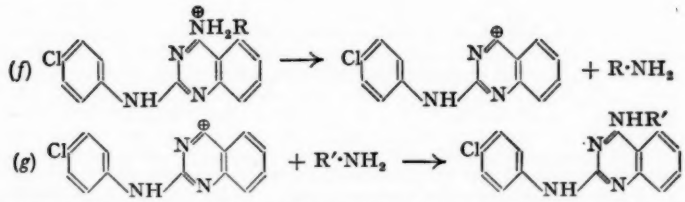
2 : 4-Dichloroquinazoline reacted with *p*-chloroaniline in cold aqueous suspension to give a compound which could not be satisfactorily purified but whose reactions showed it to be essentially 2-chloro-4-*p*-chloroanilinoquinazoline (XI; X = NH) since it condensed with *γ*-diethylaminopropylamine to give 4-*p*-chloroanilino-2-*γ*-diethylaminopropylaminoquinazoline (II; R = Cl, R′ = $[CH_2]_3$·NEt_2), and with *γ*-piperidinopropylamine to give the corresponding *γ*-piperidinopropylamino-derivative (II; R = Cl, R′ = $[CH_2]_3$·N$<[CH_2]_4>CH_2$). However, when (XI; X = NH) was heated with β-diethylaminoethylamine some of the expected 4-*p*-chloroanilino-2-β-diethylaminoethylaminoquinazoline (II; R = Cl, R′ = $[CH_2]_2$·NEt_2) was formed, but the major product proved to be 2 : 4-*bis*-β-*diethylaminoethylaminoquinazoline* (XII; R = $[CH_2]_2$·NEt_2) identical with that prepared from 2-chloro-4-β-diethylaminoethylaminoquinazoline and β-diethylaminoethylamine. The course of the reaction leading to (XII; R = $[CH_2]_2$·NEt_2) clearly involves displacement of the arylamino-residue from (XI; X = NH). Again, 2 : 4-dichloroquinazoline and sodium *p*-chlorothiophenoxide in ether gave 2-*chloro*-4-p-*chlorophenylthioquinazoline* (XI; X = S), and when this was boiled in alcoholic solution with β-diethylaminoethylamine two products were formed. One of these, separated by its insolubility in dilute acetic acid, proved to be 2 : 4-*bis*-p-*chlorophenylthioquinazoline* (XIII; X = S) and must have been formed by reaction of displaced *p*-chlorothiophenol with unaltered starting material. The second product, which was soluble in dilute acetic acid, proved to be not the expected 2-β-diethylaminoethylamino-4-*p*-chlorophenylthioquinazoline (VI; R = Cl, R′ = $[CH_2]_2$·NEt_2) but the isomeric 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline (V; R = Cl, R′ = $[CH_2]_2$·NEt_2). None of the former was isolated, and the amount formed must indeed have been very small in view of the yield of the latter and the substantial quantity of 2 : 4-bis-*p*-chlorophenylthioquinazoline also produced. A similar result was obtained starting with *γ*-diethylaminopropylamine, the products being 4-*γ*-diethylaminopropylamino-2-*p*-chlorophenylthioquinazoline (V; R = Cl, R′ = $[CH_2]_3$·NEt_2) and 2 : 4-bis-*p*-chlorophenylthioquinazoline. These results at first suggested that the initial reaction between 2 : 4-dichloroquinazoline and *p*-chlorothiophenol had taken the unexpected course to give not 2-chloro-4-*p*-chlorophenylthioquinazoline (XI; X = S) but its 4 : 2-isomer (XIV). This was proved not to be the case, however, since 2-chloro-4-hydroxyquinazoline condensed with *p*-chlorothiophenol gave 4-*hydroxy*-2-p-*chlorophenylthioquinazoline*, and this with phosphoryl chloride afforded 4-*chloro*-2-p-*chlorophenylthioquinazoline* (XIV) distinct from the isomer formed from 2 : 4-dichloroquinazoline and *p*-chlorothiophenol. Further proof of the assigned structures was provided by the conversion of each isomer into 2 : 4-bis-*p*-chlorophenylthioquinazoline

(XIII; X = S) on reaction with *p*-chlorothiophenol, and the observation that 4-chloro-2-*p*-chlorophenylthioquinazoline reacted with β-diethylaminoethylamine to give 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline (V; R = Cl, R′ = $[CH_2]_2$·NEt_2).

Some light was thrown on these displacement reactions by the fact that 2 : 4-bis-*p*-chlorophenylthioquinazoline heated with β-diethylaminoethylamine in alcoholic solution gave 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline (V; R = Cl, R′ = $[CH_2]_2$·NEt_2) with liberation of *p*-chlorothiophenol. This clearly demonstrated the lability of the 4-*p*-chlorophenylthio-group and further suggested that the formation of (V; R = Cl, R′ = $[CH_2]_2$·NEt_2) from 2-chloro-4-*p*-chlorophenylthioquinazoline and β-diethylaminoethylamine proceeded partially through the bis-*p*-chlorophenylthio-compound (XIII; X = S) as intermediate, so that the reactions (*a*) to (*d*) may be presumed to occur. Further it was shown that 2-β-diethylaminoethylamino-4-*p*-chlorophenylthioquinazoline (but not its 4 : 2-isomer) reacted with β-diethylaminoethylamine to give 2 : 4-bis-β-diethylaminoethylaminoquinazoline (XII; R = $[CH_2]_2$·NEt_2), and since this compound was not formed during the reaction between 2-chloro-4-*p*-chlorophenylthioquinazoline and β-diethylaminoethylamine the expected reaction (*e*) can only have occurred to a negligible extent.

(*a*) (XI; X = S) + NH_2·$[CH_2]_2$·NEt_2 ⟶ (X; R = $[CH_2]_2$·NEt_2) + *p*-HS·C_6H_4Cl
(*b*) (X; R = $[CH_2]_2$·NEt_2) + *p*-HS·C_6H_4Cl ⟶ (V; R = Cl, R′ = $[CH_2]_2$·NEt_2)
(*c*) (XI; X = S) + *p*-HS·C_6H_4Cl ⟶ (XIII; X = S)
(*d*) (XIII; X = S) + NH_2·$[CH_2]_2$·NEt_2 ⟶ (V; R = Cl, R′ = $[CH_2]_2$·NEt_2)
(*e*) (XI; X = S) + NH_2·$[CH_2]_2$·NEt_2 ⟶ (VI; R = Cl, R′ = $[CH_2]_2$·NEt_2)

The facile displacement of *p*-chlorothiophenol from, and its reaction with a further molecule of, 2-chloro-4-*p*-chlorophenylthioquinazoline was also demonstrated by the isolation of appreciable quantities of 2 : 4-bis-*p*-chlorophenylthioquinazoline when (XI; X = S) was boiled with alcoholic sodium hydroxide solution. Here the sodium hydroxide must be assumed to act in the same manner as the strongly basic dialkylaminoalkylamines in the reactions described above. By contrast, no reaction was detected when either 4-β-diethylaminoethylamino-2-*p*-chlorophenylthio- or 2 : 4-bis-β-diethylaminoethylamino-quinazoline was boiled with an alcoholic solution of *p*-chlorothiophenol.



Finally, a further example of the replacement of a 4-arylamino-residue may be recorded. When the hydrochloride of 2 : 4-bis-*p*-chloroanilinoquinazoline (XIII; X = NH) (prepared from 2 : 4-dichloroquinazoline and *p*-chloroaniline in chloroform solution, cf. Part XIV) was heated with β-diethylaminoethylamine some 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline (I; R = Cl, R′ = $[CH_2]_2$·NEt_2) was formed. The same product was obtained when the hydrochloride of 2-*p*-chloroanilino-4-β-hydroxyethylaminoquinazoline was heated with β-diethylaminoethylamine, in this case with displacement of a 4-alkylamino-residue. It seems possible that these displacements of 4-arylamino- and 4-alkylamino-residues may involve dissociation of a quinazolinium ion followed by recombination with a different amine, as in reactions (*f*) and (*g*), since no interaction was observed between 2 : 4-bis-*p*-chloroanilinoquinazoline (XIII; X = NH) and β-diethylaminoethylamine in the absence of hydrochloric acid. Certainly it would seem that these displacement reactions involving amino-residues differ in both facility and the necessary experimental conditions from those involving arylthio-groups.

Experimental.

2-β-Diethylaminoethylamino-4-hydroxyquinazoline (VIII; R = $[CH_2]_2$·NEt_2).—2-Chloro-4-hydroxyquinazoline (6·1 g.) and β-diethylaminoethylamine (5 c.c.) were heated for 1 hour at 140°. Excess of amine was then removed under diminished pressure. The residue was dissolved in hot acetic acid (20 c.c.) and poured into water, the solution made alkaline with sodium carbonate, and the liberated oil extracted with benzene. Evaporation of the dried extract and distillation of the residue in a high vacuum (0·001 mm.) from a bath at 188—195° gave the *product* as a colourless glass of indefinite m. p. (Found: C, 64·2; H, 7·7. $C_{14}H_{20}ON_4$ requires C, 64·6; H, 7·7%). On melting with a little water it formed a *hydrate* which crystallised from benzene–light petroleum (b. p. 60—80°) as colourless needles, m. p. 96—98° (Found: C, 60·7; H, 7·6. $C_{14}H_{20}ON_4,H_2O$ requires C, 60·4; H, 7·9%).

2-*γ-Diethylaminopropylamino*-4-*hydroxyquinazoline* (VIII; R = $[CH_2]_3$·NEt_2), prepared in a similar manner using γ-diethylaminopropylamine in place of β-diethylaminoethylamine and distilled from a bath at 185—190° under 0·001 mm., formed a colourless glass of indefinite m. p. (Found: C, 64·9; H, 8·3. $C_{15}H_{22}ON_4$ requires C, 65·7; H, 8·0%). The *hydrate* crystallised from light petroleum (b. p. 80—100°) as colourless laminæ, m. p. 96—97° (Found: C, 61·4; H, 8·6; N, 18·9. $C_{15}H_{22}ON_4,H_2O$ requires C, 61·5; H, 8·2; N, 19·2%).

2-*γ-Piperidinopropylamino*-4-*hydroxyquinazoline* (VIII; R = $[CH_2]_3$·N< $[CH_2]_4$ >CH_2).—2-Chloro-4-hydroxyquinazoline (4·5 g.) and γ-piperidinopropylamine (5 c.c.) were mixed, and when the resulting exothermic reaction had subsided the mixture was heated at 140—150° for 3·5 hours. The melt was dissolved in acetic acid (20 c.c.), and the solution poured into water (600 c.c.), treated with carbon, filtered, and made alkaline with ammonia. The precipitated product hardened on standing and was collected, dried, and crystallised from benzene–light petroleum (b. p. 60—80°) to give the *hemihydrate* as a microcrystalline solid, m. p. 117—119° (Found: C, 64·7; H, 7·5; N, 18·6; loss in a vacuum at 100°, 3·3. $C_{16}H_{22}ON_4,0·5H_2O$ requires C, 65·0; H, 7·8; N, 19·0; H_2O, 3·5%).

2-*γ-Di*-n-*butylaminopropylamino*-4-*hydroxyquinazoline* (VIII; R = $[CH_2]_3$·NBu^n_2).—Prepared in a similar manner, the *hemihydrate* crystallised from aqueous methanol as faintly yellow plates, m. p. 103—104° (Found: C, 67·0, 67·3; H, 9·0, 9·1; N, 16·8. $C_{19}H_{30}ON_4,0·5H_2O$ requires C, 67·2; H, 9·1; N, 16·5%).

4-*Chloro*-2-β-*diethylaminoethylaminoquinazoline* (IX; R = $[CH_2]_2$·NEt_2).—2-β-Diethylaminoethylamino-4-hydroxyquinazoline (8·1 g.) and phosphoryl chloride (25 c.c.) were refluxed for 1 hour, excess of phosphoryl chloride removed under reduced pressure, the residue poured on ice, and the solution treated with carbon and filtered. Addition of sodium hydroxide to the filtrate precipitated an oil which was extracted with ether and the ether extract dried (Na_2SO_4) and evaporated. Distillation of the residual oil from a bath at 170—175°/0·001 mm. gave 4-*chloro*-2-β-*diethylaminoethylaminoquinazoline* (Found: C, 60·5; H, 7·3. $C_{14}H_{19}N_4Cl$ requires C, 60·3; H, 6·8%). It formed a *sesquipicrate* which crystallised from acetic acid in large yellow needles, m. p. 205° (Found: C, 45·0; H, 4·2. $2C_{14}H_{19}N_4Cl,3C_6H_3O_7N_3$ requires C, 44·4; H, 3·8%).

4-*Chloro*-2-*γ-diethylaminopropylaminoquinazoline* (IX; R = $[CH_2]_3$·NEt_2), prepared similarly from 2-γ-diethylaminopropylamino-4-hydroxyquinazoline, formed a yellowish oil, b. p. 210—212°/0·2 mm. (Found: C, 61·8; H, 7·1. $C_{15}H_{21}N_4Cl$ requires C, 61·5; H, 7·2%).

4-*Chloro*-2-*γ-piperidinopropylaminoquinazoline* (IX; R = $[CH_2]_3$·N<$[CH_2]_4$ >CH_2), prepared in a corresponding manner from (VIII; R = $[CH_2]_3$·N < $[CH_2]_4$ > CH_2) and phosphoryl chloride, had b. p. 190—195°/0·15 mm. and then crystallised from light petroleum (b. p. 80—100°) as colourless plates, m. p. 71° (Found: N, 18·1. $C_{16}H_{21}N_4Cl$ requires N, 18·4%).

4-*Chloro*-2-*γ-di*-n-*butylaminopropylaminoquinazoline* (IX; R = $[CH_2]_3$·NBu^n_2).— 2-γ-Di-*n*-butylaminopropylamino-4-hydroxyquinazoline (5 g.) and phosphoryl chloride (15 c.c.) were heated under reflux for 1·25 hours at 120—130°. The mixture was poured on to a vigorously stirred mixture of ice (400 g.), 10N-sodium hydroxide (100 c.c.), and chloroform (100 c.c.), and, after being filtered, the chloroform layer was separated, washed with water, and dried (Na_2SO_4). The chloro-compound which remained on evaporation of the chloroform decomposed when its distillation was attempted. It was characterised as its *sesquipicrate*; microcrystalline nodules from alcohol, m. p. 157—159° (Found: C, 47·9; H, 4·8; N, 16·8. $2C_{19}H_{29}N_4Cl,3C_6H_3O_7N_3,H_2O$ requires C, 47·9; H, 4·9; N, 17·0%).

2-*Chloro*-4-p-*chloroanilinoquinazoline* (XI; X = NH).—2:4-Dichloroquinazoline (20 g.) and *p*-chloroaniline (12·8 g.), both finely powdered, were stirred at room temperature with a solution of sodium acetate (14 g.) in water (400 c.c.). After 24 hours, the mixture gave only a faint reaction for *p*-chloroaniline which was undiminished after 48 hours. The white solid was then collected, and washed with dilute hydrochloric acid and then with water. It became yellow on the surface when dried and melted at 210—215° (Found: Cl, 22·4. $C_{14}H_9N_3Cl_2$ requires Cl, 24·5%). Crystallisation from alcohol, 2-ethoxyethanol, *cyclo*hexane, or dimethylformamide, or sublimation in a high vacuum, either gave a less pure *product* or caused gross decomposition.

4-p-*Chloroanilino*-2-β-*diethylaminoethylaminoquinazoline* (II; R = Cl, R′ = $[CH_2]_2$·NEt_2).—4-Chloro-2-β-diethylaminoethylaminoquinazoline (5·8 g.) and *p*-chloroaniline (5 g.) were heated at 130—140° for 2 hours. The cooled melt was dissolved in acetic acid (30 c.c.), and the solution diluted with water (300 c.c.) and saturated with sodium acetate. Excess of *p*-chloroaniline was removed by filtration and extraction with ether, and the product precipitated from the aqueous layer by addition of ammonia. Isolated by extraction with chloroform, the base was obtained as an oil (6 g.) which afforded a *dihydrochloride* on treatment in acetone solution (100 c.c.) with 35% alcoholic hydrogen chloride (4·5 c.c.). This derivative crystallised from alcohol as colourless platelets, m. p. 262—263° (Found: C, 54·0; H, 5·9; N, 15·6, 15·7. $C_{20}H_{24}N_5Cl,2HCl$ requires C, 54·2; H, 5·9; N, 15·8%) (6223). The *dipicrate* separated from 2-ethoxyethanol as a yellow microcrystalline powder, m. p. 232—233° (Found: C, 46·3; H, 3·7; N, 18·7. $C_{20}H_{24}N_5Cl,2C_6H_3O_7N_3$ requires C, 46·4; H, 3·6; N, 18·6%).

4-p-*Chloroanilino*-2-*γ-diethylaminopropylaminoquinazoline* (II; R = Cl, R′ = $[CH_2]_3$·NEt_2).—(*a*) Prepared in a corresponding manner from 4-chloro-2-γ-diethylaminopropylaminoquinazoline and *p*-chloroaniline, the *base* crystallised from light petroleum (b. p. 100—120°) as colourless prisms, m. p. 107—108° (Found: C, 65·9; H, 7·2; N, 18·2. $C_{21}H_{26}N_5Cl$ requires C 65·7; H, 6·8; N, 18·3%) (3755).

(*b*) 2-Chloro-4-*p*-chloroanilinoquinazoline (10 g.) and γ-diethylaminopropylamine (6·5 c.c.) were heated under reflux for 2 hours at 120—130°. The resulting mixture was extracted with boiling 10% acetic acid (200 c.c.), and the solution made alkaline with ammonia and extracted with ether. Evaporation of the dried ethereal extract left a glass (2 g.) which gradually crystallised and then separated from light petroleum (b. p. 100—120°). It had m. p. 107—108° undepressed in admixture with material made by method (*a*).

4-p-*Methoxyanilino*-2-*γ-diethylaminopropylaminoquinazoline* (II; R = OMe, R′ = $[CH_2]_3$·NEt_2).—4-Chloro-2-γ-diethylaminopropylaminoquinazoline (2·6 g.) and *p*-anisidine (5 g.) were heated for 2 hours at 130—140°. A solution of the cooled melt in acetic acid (15 c.c.) was poured into 2% sodium acetate solution (200 c.c.), and the solution treated with carbon, filtered, and extracted with ether to remove

p-anisidine. The aqueous layer was made alkaline with ammonia and extracted with ether, and the extract dried and evaporated. The residue was extracted with boiling light petroleum (b. p. 100—120°), and the undissolved portion dissolved in acetone (50 c.c.) and treated with 35% alcoholic hydrogen chloride (3 c.c.). On standing, the *dihydrochloride* separated and was purified by crystallisation from alcohol–ethyl acetate. It formed a colourless microcrystalline solid, m. p. 228—230° (Found: C, 54·0; H, 7·0; N, 14·2. $C_{22}H_{29}ON_5,2HCl$ requires C, 54·0; H, 7·2; N, 14·4%) (6315).

4-p-*Chloroanilino*-2-γ-*piperidinopropylaminoquinazoline* (II; R = Cl, R′ = $[CH_2]_3{\cdot}N<[CH_2]_4>CH_2$).—(*a*) 4-Chloro-2-γ-piperidinopropylaminoquinazoline (2 g.), *p*-chloroaniline hydrochloride (1·1 g.), water (10 c.c.), and 10N-hydrochloric acid (0·1 c.c.) were boiled under reflux for 1 hour. The solution was then diluted further with water (10 c.c.), sodium acetate (2 g.) added, and the solution treated with carbon, filtered, and made alkaline with ammonia. The precipitated solid was collected, dried, and crystallised from light petroleum (b. p. 80—100°) to give the *base* as colourless platelets, m. p. 129° (Found: N, 17·3. $C_{22}N_{26}N_5Cl$ requires N, 17·7%). The *dihydrochloride*, prepared from the base in acetone solution with alcoholic hydrogen chloride, separated as a colourless microcrystalline powder, m. p. 238—240° (Found: Cl′, 15·0. $C_{22}H_{26}N_5Cl,2HCl$ requires Cl′, 15·15%) (6234). The base formed a picrate which separated from 2-ethoxyethanol–alcohol as small yellow plates, m. p. 228—229°.

(*b*) 2-Chloro-4-*p*-chloroanilinoquinazoline (6 g.) and γ-piperidinopropylamine (5 c.c.) were heated at 130—140° under reflux for 3 hours. The cooled melt was extracted with boiling 20% acetic acid (150 c.c.), and the cooled, filtered extract made faintly alkaline with ammonia to precipitate the *acetate* which crystallised from ethyl acetate as colourless square plates, m. p. 114—115° (Found: C, 60·5; H, 7·0; N, 14·8; Cl, 7·5. $C_{22}H_{26}N_5Cl,CH_3{\cdot}CO_2H,H_2O$ requires C, 60·75; H, 6·8; N, 14·8; Cl, 7·5%). The free base liberated from this acetate with sodium hydroxide and crystallised from light petroleum (b. p. 80—100°) had m. p. 129° undepressed in admixture with base made by method (*a*).

4-p-*Chloroanilino*-2-γ-*di*-n-*butylaminopropylaminoquinazoline* (II; R = Cl, R′ = $[CH_2]_3{\cdot}NBu^n_2$).—Prepared from 4-chloro-2-γ-di-*n*-butylaminopropylaminoquinazoline and *p*-chloroaniline as described above for 4-*p*-methoxyanilino-2-γ-diethylaminopropylaminoquinazoline, the *dihydrochloride* separated from ethyl acetate and a little alcohol as a colourless microcrystalline powder, m. p. 125—126° (Found: C, 56·4; H, 7·4; N, 12·9. $C_{25}H_{34}N_5Cl,2HCl,H_2O$ requires C, 56·5; H, 7·15; N, 13·2%) (6277).

2-β-*Diethylaminoethylamino*-4-p-*chlorophenylthioquinazoline* (VI; R = Cl, R′ = $[CH_2]_2{\cdot}NEt_2$).—4-Chloro-2-β-diethylaminoethylaminoquinazoline (4·5 g.) and *p*-chlorothiophenol (4·5 g.) were heated to 130° by means of an oil-bath. When the vigorous reaction had subsided the mixture was cooled and dissolved in acetic acid (20 c.c.), and the solution poured on a mixture of ice and water. The unchanged *p*-chlorothiophenol thereby precipitated was filtered off and washed with water, and the united filtrates made alkaline with sodium hydroxide. The precipitated product was collected, washed with water, dried, and crystallised from light petroleum (b. p. 60—80°), giving 2-β-*diethylaminoethylamino*-4-p-*chlorophenylthioquinazoline* as yellow needles (yield, 2·1 g.), m. p. 92° (Found: C, 61·9; H, 5·8; S, 8·6. $C_{20}H_{23}N_4ClS$ requires C, 62·1; H, 5·9; S, 8·3%) (6225).

2-γ-*Diethylaminopropylamino*-4-p-*chlorophenylthioquinazoline* (VI; R = Cl, R′ = $[CH_2]_3{\cdot}NEt_2$), prepared in a corresponding manner from 4-chloro-2-γ-diethylaminopropylaminoquinazoline and *p*-chlorothiophenol, crystallised from light petroleum (b. p. 60—80°) as pale yellow rhombs, m. p. 100° (Found: C, 62·6; H, 6·2. $C_{21}H_{25}N_4ClS$ requires C, 62·9; H, 6·2%) (6224).

4-γ-*Diethylaminopropylamino*-2-p-*chlorophenylthioquinazoline* (V; R = Cl, R′ = $[CH_2]_3{\cdot}NEt_2$).—2-Chloro-4-γ-diethylaminopropylaminoquinazoline hydrate (15 g.) (Part XIV) and *p*-chlorothiophenol (15 g.) were fused at 120—130° for 3 hours and the mixture worked up as described above for 2-β-diethylaminoethylamino-4-*p*-chlorophenylthioquinazoline. The *product* crystallised from benzene–light petroleum (b. p. 60—80°) as fine colourless needles (yield, 12·0 g.), m. p. 96° (Found: C, 63·2; H, 5·8; S, 8·6. $C_{21}H_{25}N_4ClS$ requires C, 62·9; H, 6·2; S, 8·0%) (5379).

4-γ-*Diethylaminopropylamino*-2-p-*tolylthioquinazoline* (V; R = Me, R′ = $[CH_2]_3{\cdot}NEt_2$), similarly prepared from (X; R = $[CH_2]_3{\cdot}NEt_2$) and thio-*p*-cresol, crystallised from light petroleum (b. p. 60—80°) or ether as colourless needles, m. p. 121° (Found: C, 69·6; H, 7·3; N, 15·1. $C_{22}H_{28}N_4S$ requires C, 69·5; H, 7·4; N, 14·75%) (3759).

4-β-*Diethylaminoethylamino*-2-p-*chlorophenylthioquinazoline* (V; R = Cl, R′ = $[CH_2]_2{\cdot}NEt_2$), prepared in a corresponding manner, separated from light petroleum (b. p. 80—100°) as large colourless needles, m. p. 123° (Found: C,62·4; H, 6·4; S, 8·2. $C_{20}H_{23}N_4ClS$ requires C, 62·1; H, 5·9, S, 8·3%) (5331).

2 : 4-*Bis*-β-*diethylaminoethylaminoquinazoline* (XII; R = $[CH_2]_2{\cdot}NEt_2$).—2-Chloro-4-β-diethylaminoethylaminoquinazoline hydrate (5·6 g.) and β-diethylaminoethylamine (2·5 c.c.) were heated for 2 hours at 130°, the mixture cooled and dissolved in dilute acetic acid, and the filtered solution basified with sodium hydroxide. The liberated oil was extracted with benzene, and the dried extract evaporated. Distillation of the residual oil gave the *product* (yield, 2·8 g.) as a pale yellow oil, b. p. 230—232°/0·1 mm. (Found: C, 66·5; H, 9·4. $C_{20}H_{34}N_6$ requires C, 67·1; H, 9·5%). It formed a *tripicrate* which was obtained in two distinct modifications: the first had m. p. 193—194° after two crystallisations from acetic acid (Found: C, 43·8; H, 4·3. $C_{20}H_{34}N_6,3C_6H_3O_7N_3$ requires C, 43·7; H, 4·1%); and the second had m. p. 213—214°, also from acetic acid (Found: C, 43·9, H, 4·5%), and was formed from the first on standing in contact with the solution. The *trihydrochloride* (6291) was obtained by dissolving the base (2·3 g.) in acetone (30 c.c.) and adding 35% alcoholic hydrogen chloride (2 c.c.). It separated first as an oil which crystallised on scratching, and after being collected and washed with acetone crystallised from alcohol as colourless prisms, m. p. 191—192° (Found: C, 49·3; H, 7·5; N, 16·9; Cl, 21·9. $C_{20}H_{34}N_6,3HCl,H_2O$ requires C, 49·45; H, 8·0; N, 17·3; Cl, 21·9%).

Condensation of 2-*Chloro*-4-p-*chloroanilinoquinazoline with* β-*Diethylaminoethylamine.*—2-Chloro-4-*p*-chloroanilinoquinazoline (6 g.) and β-diethylaminoethylamine (5 c.c.) were heated under reflux for 3·5 hours at 120—130°. The cooled melt was extracted with boiling 10% acetic acid (120 c.c.), and the solution made alkaline with ammonia and extracted with ether. After drying, the ethereal extract was evaporated, and unchanged β-diethylaminoethylamine removed at 150—160°/15 mm. *p*-Chloroaniline was detected in the residue and was removed by ether extraction of a solution in 10% acetic acid containing sodium acetate (5 g.). The acid solution was then basified with sodium hydroxide, and the product

isolated by ether extraction. The residue obtained on evaporation of the dried ether extract was dissolved in acetone (40 c.c.), and 35% alcoholic hydrogen chloride (2 c.c.) added. The resulting oil solidified on scratching, and was then collected and crystallised from alcohol, giving 2 : 4-bis-β-diethylaminoethylaminoquinazoline trihydrochloride, m. p. and mixed m. p. 191—192°. Concentration of the acetone–alcoholic mother liquors afforded an impure hydrochloride which was converted into the base and thence into the picrate. Crystallisation of this picrate first from acetic acid and then from 2-ethoxyethanol afforded 4-*p*-chloroanilino-2-β-diethylaminoethylaminoquinazoline dipicrate, m. p. 230—232° undepressed in admixture with authentic material (see above).

2-*Chloro*-4-p-*chlorophenylthioquinazoline* (XI; X = S).—*p*-Chlorothiophenol (5·8 g.) was added to a solution of sodium (1·0 g.) in alcohol (50 c.c.), the solvent evaporated, and the dried residue ground to a fine powder. This sodium salt, suspended in dry ether (100 c.c.), was shaken with powdered 2 : 4-dichloroquinazoline (8·0 g.) for 4 hours and the mixture left overnight. Water (50 c.c.) and 10N-sodium hydroxide (10 c.c.) were added, the ether removed under diminished pressure at room temperature, and the solid collected, washed with water, and dried. Crystallised from light petroleum (b. p. 120—140°), 2-*chloro*-4-p-*chlorophenylthioquinazoline* formed large colourless needles, m. p. 156—157° (Found : C, 54·8; H, 2·9; S, 10·3. $C_{14}H_8N_2Cl_2S$ requires C, 54·7; H, 2·6; S, 10·4%).

4-*Hydroxy*-2-p-*chlorophenylthioquinazoline*.—2-Chloro-4-hydroxyquinazoline (3·6 g.) and *p*-chlorothiophenol (2·9 g.) were heated with stirring to 100°. The solid mass resulting from the vigorous reaction was cooled, powdered, and heated at 100° for a further hour, then cooled and crystallised directly from chlorobenzene, giving the *product* as colourless slender needles (yield, 5·2 g.), m. p. 246° (Found : C, 58·4; H, 3·2; S, 11·2. $C_{14}H_9ON_2ClS$ requires C, 58·2; H, 3·1; S, 11·2%). When this compound was crystallised from 2-ethoxyethanol only pearly leaflets of 2 : 4-dihydroxyquinazoline, m. p. 340°, were obtained.

4-*Chloro*-2-p-*chlorophenylthioquinazoline* (XIV).—The preceding compound (3·0 g.) and phosphoryl chloride (15 c.c.) were refluxed for 15 minutes, the mixture poured on ice, and the solid *product* collected, dried, and crystallised from light petroleum (b. p. 80—100°), giving colourless needles (yield, 1·8 g.), m. p. 126° (Found : C, 54·7; H, 2·8; S, 10·1. $C_{14}H_8N_2Cl_2S$ requires C, 54·7; H, 2·6; S, 10·4%).

2 : 4-*Bis*-p-*chlorophenylthioquinazoline* (XIII; X = S).—(*a*) 2-Chloro-4-*p*-chlorophenylthioquinazoline (3·1 g.) and *p*-chlorothiophenol (1·5 g.) were powdered together and heated in an oil-bath at 100°; a vigorous reaction ensued. The melt was cooled, powdered, and reheated at 100° for 1 hour. Crystallisation from xylene–light petroleum (b. p. 80—100°) then gave the *product* as clumps of colourless prisms (yield, 3·3 g.), m. p. 134—135° (Found : S, 15·7; Cl, 16·7. $C_{20}H_{12}N_2Cl_2S_2$ requires S, 15·4; Cl, 17·1%).

(*b*) The product from the interaction of 4-chloro-2-*p*-chlorophenylthioquinazoline (1·2 g.) and *p*-chlorothiophenol (0·6 g.) was worked up as in (*a*) to give the same compound, m. p. and mixed m. p. 134—136° (Found : S, 15·8%).

Condensation of 4-*Chloro*-2-p-*chlorophenylthioquinazoline with β-Diethylaminoethylamine*.—A solution of the chloroquinazoline (1·0 g.) and β-diethylaminoethylamine (0·5 g.) in alcohol (15 c.c.) was boiled for 2 hours, the solvent evaporated, and the residue treated with sodium hydroxide and extracted with ether. After evaporation of the ether extract the residue was dissolved in acetic acid (10 c.c.), poured into water (100 c.c.), and basified with sodium hydroxide. The precipitated solid was collected, dried, and crystallised from light petroleum (b. p. 60—80°) to give 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline (yield, 0·8 g.), m. p. and mixed m. p. 122° (Found : C, 61·7; H, 5·9; S, 8·8%).

Condensation of 2-*Chloro*-4-p-*chlorophenylthioquinazoline with β-Diethylaminoethylamine*.—A solution of the chloroquinazoline (XI; X = S) (6·0 g.) and β-diethylaminoethylamine (2·4 g.) in alcohol (100 c.c.) was boiled for 2 hours, and the solvent evaporated under reduced pressure and dissolved in hot acetic acid (50 c.c.). On addition of this solution to ice and water (500 c.c.) a solid was precipitated. This was collected, washed with water, and dried at 100° (yield, 1·4 g.) followed by crystallisation from light petroleum (b. p. 80—100°) to give colourless needles of 2 : 4-bis-*p*-chlorophenylthioquinazoline, m. p. and mixed m. p. 134—136° (Found : S, 15·7; Cl, 16·9%). The acetic acid filtrate from the above compound was basified with 10N-sodium hydroxide, and the precipitated product collected, washed with water, and dried at 80° (yield, 4·4 g., m. p. 120°). Crystallised from light petroleum (b. p. 60—80°), it formed colourless flat needles, m. p. 122° undepressed in admixture with 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline prepared as described above (Found : C, 62·4; H, 5·8%).

Condensation of 2-*Chloro*-4-p-*chlorophenylthioquinazoline and γ-Diethylaminopropylamine*.—A solution of γ-diethylaminopropylamine (2·5 g.) and (XI; X = S) (5·2 g.) in alcohol (85 c.c.) was boiled for 2 hours and then worked up as in the preceding experiment. The products isolated were 2 : 4-bis-*p*-chlorophenylthioquinazoline (0·8 g.), m. p. and mixed m. p. 135—136° (Found : S, 15·5%), and 4-γ-diethylaminopropylamino-2-*p*-chlorophenylthioquinazoline (1·8 g.), m. p. 94° undepressed in admixture with authentic material prepared as described above (Found : S, 8·0%).

Condensation of 2 : 4-*Bis*-p-*chlorophenylthioquinazoline with β-Diethylaminoethylamine*.—A solution of (XIII; X = S) (2·1 g.) and β-diethylaminoethylamine (0·6 g.) in alcohol (25 c.c.) and 2-ethoxyethanol (10 c.c.) was heated on the steam-bath for 6 hours and the solvent then removed under diminished pressure. The distillate was treated with 10N-sodium hydroxide (1 c.c.) and again evaporated, the residue dissolved in a little water, and the solution filtered (carbon) and acidified, giving colourless shining leaflets of *p*-chlorothiophenol (0·5 g.), m. p. 50—52°. The residue from the initial distillation was dissolved in acetic acid (10 c.c.), the solution poured into water, and the solid collected, dried, and crystallised from light petroleum (b. p. 80—100°), giving unchanged 2 : 4-bis-*p*-chlorophenylthioquinazoline (0·4 g.), m. p. and mixed m. p. 135—136° (Found : S, 15·5%). The acetic acid filtrate from this material was basified with sodium hydroxide solution, and the precipitated solid collected, dried, and purified by crystallisation from light petroleum (b. p. 80—100°). It was identified as 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline (yield, 1·3 g.), m. p. and mixed m. p. 123—124° (Found : S, 8·7%).

Condensation of 2-β-*Diethylaminoethylamino*-4-p-*chlorophenylthioquinazoline and β-Diethylaminoethylamine*.—The quinazoline (1·6 g.), β-diethylaminoethylamine (1·2 c.c.), and alcohol (10 c.c.) were refluxed for 24 hours and the solvent removed under diminished pressure. The residue was dissolved in hot acetic acid (10 c.c.), the solution poured into water (100 c.c.), and the precipitated solid collected.

This was purified by dissolution in dilute sodium hydroxide and reprecipitation with acetic acid to give *p*-chlorothiophenol (0·25 g.), m. p. and mixed m. p. 54°. The acetic acid filtrate from the original isolation of this material was made strongly alkaline with sodium hydroxide and the precipitated oil extracted with benzene. Evaporation of the dried benzene extract left an oil (free from sulphur) which was purified by vacuum distillation (b. p. 220—224°/0·1 mm.) and identified as 2 : 4-bis-β-diethylaminoethylaminoquinazoline. With picric acid in alcoholic solution it afforded a picrate which crystallised from acetic acid in large yellow needles, m. p. 213—214° undepressed in admixture with authentic picrate (see above) (Found : C, 43·4; H, 4·1%).

When 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline (1·6 g.) was used in a similar experiment in place of its 2 : 4-isomer it was recovered unchanged (1 g., m. p. 122°) (Found : S, 8·4%). No *p*-chlorothiophenol was detected.

Action of Sodium Hydroxide on 2-*Chloro*-4-p-*chlorophenylthioquinazoline.*—2-Chloro-4-*p*-chlorophenylthioquinazoline (3·1 g.) was added to a solution of sodium hydroxide (0·4 g.) in alcohol (25 c.c.) and water (10 c.c.), and the solution refluxed for 4 hours. It was then poured into water, and the precipitated solid collected, dried, and crystallised from light petroleum (b. p. 60—80°) to give 2 : 4-bis-*p*-chlorophenylthioquinazoline (0·9 g.), m. p. and mixed m. p. 134—135° (Found: C, 57·9; H, 3·2; N, 6·8. Calc. for $C_{20}H_{12}N_2Cl_2S_2$: C, 57·8; H, 2·9; N, 6·7%).

Attempted Reaction of 4-β-*Diethylaminoethylamino*-2-p-*chlorophenylthioquinazoline with* p-*Chlorothiophenol.*—The quinazoline (1·9 g.) and *p*-chlorothiophenol (1·5 g.) in alcohol (50 c.c.) were heated on the steam-bath for 10 hours. When worked up by evaporation and treatment with dilute acetic acid, only unchanged 4-β-diethylaminoethylamino-2-*p*-chlorophenylthioquinazoline, m. p. and mixed m. p. 124°, was isolated.

No reaction could be detected when the condensation of 2 : 4-bis-β-diethylaminoethylaminoquinazoline and *p*-chlorothiophenol was attempted under similar conditions.

2 : 4-*Bis*-p-*chloroanilinoquinazoline* (XIII; X = NH).—2 : 4-Dichloroquinazoline (10 g.) and *p*-chloroaniline (12·75 g.) in chloroform (125 c.c.) were stirred at room temperature for 6 hours. After a further 24 hours the precipitate was collected, washed with chloroform, dried, lixiviated with water, filtered off, and washed with water to remove *p*-chloroaniline hydrochloride. It was then obtained as a greyish crystalline powder, m. p. 340—345° undepressed in admixture with the hydrochloride of material made by the method described in Part XIV.

Condensation of 2 : 4-*Bis*-p-*chloroanilinoquinazoline Hydrochloride with* β-*Diethylaminoethylamine.*—2 : 4-Bis-*p*-chloroanilinoquinazoline hydrochloride (4·3 g.) and β-diethylaminoethylamine (4 c.c.) were heated at 130—140° under reflux for 3 hours, and the mixture extracted with boiling 10% acetic acid (40 c.c.) containing sodium acetate (1 g.). When cold, the extract deposited an oil which was removed by ether extraction and identified as *p*-chloroaniline. The aqueous solution was treated with hydrochloric acid (10 c.c.) and allowed to stand. The crystalline material which separated was collected and identified as 2-*p*-chloroanilino-4-β-diethylaminoethylaminoquinazoline dihydrochloride (Part XIV), m. p. and mixed m. p. 253°.

Condensation of 2-p-*Chloroanilino*-4-β-*hydroxyethylaminoquinazoline Hydrochloride with* β-*Diethylaminoethylamine.*—2-*p*-Chloroanilino-4-β-hydroxyethylaminoquinazoline hydrochloride (2·9 g.) (Part XIV) and β-diethylaminoethylamine (3 c.c.) were heated at 130—140° for 3 hours under reflux, and the mixture cooled and extracted with hot 10% acetic acid (50 c.c.). Addition of hydrochloric acid (15 c.c.) to the filtered extract precipitated a crystalline product, m. p. 253° undepressed in admixture with authentic dihydrochloride of (I; R = Cl, R′ = $[CH_2]_2$·NEt_2).

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358. *Toxic Fluorine Compounds containing the* C–F *Link. Part I. Methyl Fluoroacetate and Related Compounds.*

By B. C. SAUNDERS and G. J. STACEY.

An account is given of the preparation and properties of methyl fluoroacetate, a convulsant poison with a delayed action. Unlike the other methyl halogenoacetates, it does not possess lachrymatory properties. Other fluorine compounds are described which are in general toxic if they contain the F·CH_2·CO· group, but non-toxic if they contain the ·COF group.

Triethyl-lead fluoroacetate combines the sternutatory properties associated with triethyl-lead salts with the convulsant action of the fluoroacetates.

THE work described in this series of papers was carried out in Cambridge during the war, and was originally submitted by us to the Ministry of Supply in communications entitled "Fluoroacetates and related compounds". These communications were made available to American workers from the inception of the work. The present paper is concerned mainly with a description of methyl fluoroacetate, CH_2F·CO_2Me, and of certain other derivatives of fluoroacetic acid.

In this vol., p. 695 *et seq.* (see also McCombie and Saunders, *Nature*, 1946, **157**, 287, 776), we have described toxic fluorine compounds containing the >POF grouping. Such compounds possessed quick knock-out action and many of them were powerful miotics. Compounds of the

" fluoroacetate " series are characterised by the $\cdot CH_2F$ group. Many of them are highly toxic, with delayed action, but are completely devoid of miotic activity. The action is that of a convulsant poison.

Methyl fluoroacetate was first prepared by Swarts (*Bull. Soc. chim.*, 1896, **15**, 1134) in small yield by the action of silver or mercurous fluoride on methyl iodoacetate. The method is quite impracticable for large-scale work and therefore the preparation was reinvestigated in detail.* Methyl chloroacetate was used in place of the expensive iodoacetate, and a variety of fluorinating agents was tried. It was found that fluorination could be effected by heating methyl chloroacetate in a rotating autoclave with potassium fluoride at 220° for 4 hours. Sodium fluoride on the other hand was almost without action.

Methyl fluoroacetate (MFA) is a liquid of b. p. 104° and f. p. *ca.* — 32° and is almost odourless. During a 10-minute exposure to a lethal concentration of the vapour, small animals did not appear to be affected in any way. After exposure, no very obvious symptoms developed until some 30—60 minutes later (depending upon the concentration). The symptoms shown depended to some extent upon the species, but all animals suffered convulsions, from which a partial recovery was sometimes made. Finally, however, a recurrence of the convulsions would cause death.

The L.C. 50 for rabbits, rats, and guinea-pigs was of the order of 0·1 mg./l. Mice were more resistant. By intravenous injection into rabbits the L.D. 50 was 0·25 mg./kg. The L.D. 50 for subcutaneous injection into mice was found to be of the order of 7—10 mg./kg. MFA was also found to be toxic by absorption through the skin, but less so than by other routes. When placed on the clipped backs of rabbits the L.D. 50 was about 20 mg./kg. Free evaporation of the drops was permitted. The animals showed the usual symptoms.

It is noteworthy that a massive concentration of the vapour of methyl chloroacetate (1 : 1,000; 4·85 mg./l.) did not kill any animals.

MFA is practically odourless. When four of us were exposed to a concentration of 1 : 1,000,000 in a 10 m.³ chamber, we were unable to detect the compound. Even at 1 : 100,000 (30 seconds for reasons of safety) the compound was found to possess only a faint fruit-like odour indistinguishable from that of many harmless esters not containing fluorine.

The fluorine atom in methyl fluoroacetate (and in many other compounds containing the $CH_2F\cdot$ group described in this series of papers) is very firmly bound. When MFA was boiled with 20% alcoholic potassium hydroxide for 5 minutes, no free fluoride was formed. Even after some 20 hours, there was only about a 50% conversion into potassium fluoride. From the inception of this work we have found the most satisfactory sensitive qualitative test for fluorine in an organic compound to consist in the formation of "oily droplets" when it is heated with a mixture of concentrated sulphuric acid and potassium dichromate.

It was obviously of interest to determine whether other esters of fluoroacetic acid would prove to be more or less toxic than the methyl ester. In the fluorophosphonate series, for example, we found that esters of secondary alcohols were far more potent than those of primary alcohols; for instance, di*iso*propyl fluorophosphonate (I) was a compound of outstanding activity (Saunders and Stacey, this vol., p. 696). Accordingly ethyl, n-*propyl*, and iso*propyl*

$(CHMe_2\cdot O)_2POF$ (I.) $CHMeF\cdot CO_2Me$ (II.) $CMe_2F\cdot CO_2Me$ (III.)

fluoroacetates were prepared by heating the corresponding esters of chloroacetic acid in the rotating autoclave with potassium fluoride. The toxicity figures of these esters were very similar to those of methyl fluoroacetate.

In the fluorophosphonate series, we found that the diphenyl ester (this vol., p. 1011) was relatively non-toxic. *Phenyl fluoroacetate*, however, was toxic with an L.D. 50 of 6—10 mg./kg. for subcutaneous injection into mice. The symptoms were similar to those displayed by methyl fluoroacetate.

It was next important to determine the effect of altering the groups adjacent to the fluorine atom. Thus *methyl α-fluoropropionate* (II) and *α-fluoro*iso*butyrate* (III) were prepared. Both these compounds were non-toxic. The first, for example, at a concentration of 1 : 20,000 (0·24 mg./l.) killed 0/23 of a batch of 3 rabbits, 4 guinea-pigs, 6 rats, and 10 mice. The second at the same concentration killed only 2/23.

In Report No. 5 on fluoroacetates to the Ministry of Supply (May 30th, 1943) we described the

* Some of the early work in connexion with methyl fluoroacetate was carried out in collaboration with F/O Sporzynski, Prof. Briscoe, and Prof. Emeléus. We acknowledge with thanks their valuable help.

preparation of *methyl* 1 : 3-*difluoroacetoacetate*, $CH_2F{\cdot}CO{\cdot}CHF{\cdot}CO_2Me$, in 10% yield by the action of sodium on methyl fluoroacetate. Later (Report No. 10, July 14th, 1944), we reported that if the condensation were carried out in the presence of methyl alcohol, the yield of methyl difluoroacetoacetate could be increased to 23%, and allowing for recovered methyl fluoroacetate the overall yield was 35%.

Fluoroacetyl chloride, $CH_2F{\cdot}COCl$, was prepared as a useful fluoroacetylating agent in synthetic work. It was interesting to compare its toxicity with the isomeric chloroacetyl fluoride. The former possessed a toxicity comparable with that of methyl fluoroacetate, whereas the latter was relatively non-toxic. This is readily understandable in that fluoroacetyl chloride gives the toxic fluoroacetic acid, whereas chloroacetyl fluoride hydrolyses to chloroacetic acid and the relatively non-toxic (at the concentrations employed) hydrogen fluoride. Fluoroacetyl fluoride also possessed a toxicity comparable with that of fluoroacetyl chloride or of methyl fluoroacetate, again showing that the ·COF group contributed practically nothing. Acetyl fluoride was also non-toxic.

Goswami and Sarkar (*J. Indian Chem. Soc.*, 1933, 537) claim to have prepared methyl and ethyl fluoroformates by the action of thallium fluoride on the corresponding chloroformates. These fluoroformates were described as powerful lachrymators. We found that no reaction took place between potassium fluoride and ethyl chloroformate in boiling carbon tetrachloride or nitrobenzene. Ethyl fluoroformate could, however, be produced by the action of potassium fluoride on ethyl chloroformate by using the autoclave technique. It was found not to have the lachrymatory properties claimed for it, and was non-toxic in comparison with MFA. This non-toxicity was to be expected, as the fluoroformate contains the ·COF and not the $CH_2F{\cdot}$ group.

Chloromethyl esters are obtained quite readily by the action of paraformaldehyde on the appropriate acid chloride in the presence of a small quantity of zinc chloride as catalyst (Ulich and Adams, *J. Amer. Chem. Soc.*, 1921, **43**, 662). It therefore seemed worth while to try the action of paraformaldehyde on fluoroacetyl fluoride, but the only product which could be isolated was a low-melting solid which appeared from its reactions to be *methylene bisfluoroacetate*, $CH_2(O{\cdot}CO{\cdot}CH_2F)_2$. The compound was submitted for physiological tests and it was shown that the L.D. 50 for subcutaneous injection into mice was about 10 mg./kg. Subcutaneous injection into rats with doses of 2·5, 5, and 10 mg./kg. all killed 1/1.

Sodium fluoroacetate was prepared with the idea of obtaining a stable water-soluble compound containing the $CH_2F{\cdot}CO{\cdot}$ group, suitable for feeding experiments. The method of obtaining this salt is new, and is described in detail in the Experimental section. It consists essentially in adding cold aqueous sodium hydroxide to methyl fluoroacetate and evaporating the solution.

Fluoroacetic anhydride, which was readily prepared by the action of fluoroacetyl chloride on sodium fluoroacetate, was a mobile liquid of b. p. 89°/12 mm. It was rather more toxic by inhalation than MFA (weight for weight).

It has been shown that trialkyl-lead salts have marked sternutatory action when dispersed as a particulate cloud (McCombie and Saunders, *Nature*, 1947, **159**, 491). *Triethyl-lead fluoroacetate*, $CH_2F{\cdot}CO_2PbEt_3$, was therefore prepared with the idea of combining sternutatory action with " fluoroacetate-like " activity. The compound, a stable, highly crystalline material, was readily prepared by the action of fluoroacetic acid on tetraethyl-lead in the presence of silica gel. As a sternutator it proved to be similar in action to that of the majority of other triethyl-lead salts of organic acids. Eight observers were exposed for 10 minutes to a nominal concentration of 1 part in 10,000,000 (*i.e.*, 1·7 mg./m.^{3}) obtained by spraying an ether–alcoholic solution of the material. They all suffered from intense irritation of the nose and throat within the first minute, and five reported pains in the chest. Subcutaneous injection into mice gave an L.D. 50 of about 15 mg./kg. and produced the usual " fluoroacetate-like " symptoms.

Glycol bisfluoroacetate was prepared with a view to obtaining a toxic fluorine compound (containing the $CH_2F{\cdot}CO$ group) which would have a high b. p. and be soluble in oils and fats. [When it was sprayed into a chamber, 4/13 animals (rats, guinea-pigs, and rabbits) were killed at 1 : 40,000 for 10 mins. and exhibited the convulsions characteristic of MFA. This low toxicity may be due to low volatility.] The compound was found to be quite soluble in hot olive oil and to form in the cold a solution of sufficient concentration for animal feeding experiments. Injection of the solution (5 mg./c.c.) into the stomach with a catheter, showed that the L.D. 50 for rats was about 2·2 mg./kg.

Cholesteryl fluoroacetate was made in an attempt to discover whether a combination of fluoroacetic acid and some biologically important compound might give a product of increased toxicity and so give some clue as to the fate of fluoroacetic acid (or of MFA) in the body. This

compound, however, placed considerable limitations upon injection experiments owing to its low solubility in non-toxic solvents. It appeared, however, to be considerably less toxic than MFA.

In view of the well-known pharmacological action of aspirin, it was thought that the fluorine analogue, O-(*fluoroacetyl*)*salicylic acid*, might be of considerable interest. The compound was readily made by acylation of salicylic acid by fluoroacetyl chloride in the presence of pyridine. The L.D. 50 for subcutaneous injection into mice was approximately 15 mg./kg. After injection the mice went into a drugged sleep, and died overnight.

Experimental.

Methyl Fluoroacetate.—Methyl chloroacetate (108·5 g., 1 mol.) and neutral anhydrous potassium fluoride (70 g., 1·2 mols.) were mixed and heated (with glass marbles) in an inclined rotating autoclave at a constant temperature. A speed of about 280 r.p.m. together with the glass marbles ensured thorough mixing. At the end of a specified time the autoclave was allowed to cool and the contents were broken up and washed out with ether, and the inorganic salts filtered off. The filtrate was then placed in a flask with an efficient fractionating column 80 cm. long. The ether was distilled off slowly. The temperature then rose rapidly to 104°, and the fraction, b. p. 104—110°, was collected (methyl fluoroacetate). The temperature again rose rapidly to 125°, and the fraction, b. p. 125—132°, was collected (unchanged methyl chloroacetate). Below are tabulated the results of experiments employing different temperatures and times. For all subsequent work the conditions of experiment No. 5 were employed.

The fraction, b. p. 104—110°, on refractionation came over almost entirely at 104·5° (Found: F, 20·65. Calc. for $C_3H_5O_2F$: F, 20·65%) (for method of fluorine analysis see Chapman, Heap, and Saunders, *Analyst*, in the press). Methyl fluoroacetate is a mobile liquid of f. p. − 32°, $d_4^{20°}$ 1·1744, $n_D^{20°}$ 1·3679, soluble in water to the extent of about 15%. Hydrolysis according to the equation $CH_2F{\cdot}CO_2CH_3 + H_2O = CH_2F{\cdot}CO_2H + CH_3{\cdot}OH$ was found to be 50% complete at room temperature in about 14 days. The ester was completely miscible with alcohol, ether, acetone, light petroleum (b. p. 40—60°), carbon tetrachloride, benzene, glacial acetic acid, and 2 : 2′-dichlorodiethyl sulphide, and partly soluble in carbon disulphide.

Expt.	Temp.	Duration (hrs.).	B. p. 104—110° (g.).	B. p. 125—132° (g.).	Residue, b. p. >132° (g.).	Wt. of inorganic salts filtered off (g.).	Yield (actual), %.	Yield (net),* %.	Remarks.
1	140°	24	1·2	85·3	5·6	70	1·3	6·1	—
2	150	20	3·6	81·3	7·7	72	3·9	15·6	—
3	160	15	5·6	78·5	6·7	73	6·1	22·0	Press. *ca.* 2 atm.
4	190	10	35	40·5	9·1	86	38·0	60·7	Press. *ca.* 10 atm.
5	220	4	50·1	4·5	9·4	99	54·5	59·6	Press. *ca.* 12 atm.; about 1 atm. in cold at end of run
6	250	2	43·8	4·8	9·6	98	37·8	39·6	Press. *ca.* 30 atm.; 4 atm. in cold at end of run

* Allowing for recovery of methyl chloroacetate.

Highest actual yield at 220°
„ net „ 190° (but of course more KF required per g. of MFA).

[N.B.—Because of the non-detectability of MFA by smell, respirators should be used when cleaning out the autoclave after a run.]

Ethyl Fluoroacetate.—Ethyl chloroacetate (122·5 g., 1 mol.) and dry potassium fluoride (70 g., 1·2 mols.) were heated in a rotating autoclave for 4 hours at 220°. The product was extracted with ether, the ether distilled off, and the residue fractionated. The fluoroacetate (20 g.) came over between 117° and 125°, the unchanged material (72·6 g.) between 125° and 144°, and a small residue (8·5 g.) was left. The fluoroacetate was redistilled and had b. p. 117—121°. It was chlorine-free (Found: F, 18·0. Calc. for $C_4H_7O_2F$: F, 17·9%).

n-*Propyl Fluoroacetate.*—The chloroacetate (cf. Shreiner, *Annalen*, 1879, **197**, 8, who gave very meagre details) was prepared as follows: Chloroacetic acid (567 g.) and *n*-propyl alcohol (540 g.) were refluxed for 6 hours with a stream of dry hydrogen chloride passing through the mixture. Two layers separated: the lower ester layer was treated with anhydrous sodium carbonate, filtered, and dried (Na_2SO_4) (A). The upper layer was saturated with sodium carbonate and separation into two layers took place; the lower of these was dried (Na_2SO_4) (B). A and B were combined and distilled; b. p. 156—158°; yield 450 g. (69·1%).

n-Propyl chloroacetate (1 mol.) and dry powdered potassium fluoride (1·2 mols.) were mixed and heated to 200° for 4½ hours in a rotating autoclave. The product was then extracted with dry ether and distilled through a 50-cm. fractionating column. The n-*propyl fluoroacetate* had b. p. 135—137° (Found: F, 15·62. $C_5H_9O_2F$ requires F, 15·8%).

iso*Propyl Fluoroacetate.*—The chloroacetate was prepared in a similar manner to the normal compound; b. p. 148·5°, yield 71%.

Thence the *fluoroacetate* was prepared by means of potassium fluoride in a rotating autoclave; b. p. 124°, yield 42% (Found: F, 15·61%).

Phenyl Fluoroacetate.—Phenol (18·8 g.) was dissolved in dry pyridine (15 c.c.) and fluoroacetyl

chloride (20 g., 5% excess) was added slowly, the temperature being kept at about 50°. The mixture was then heated on a water-bath for 10 minutes, and poured into water. Solid at once separated; yield 30 g. (100%). The *fluoroacetate* recrystallised from aqueous alcohol in lustrous colourless plates, m. p. 63·5—64·0° (Found: F, 12·45. $C_3H_7O_2F$ requires F, 12·34%).

Methyl α-Fluoropropionate.—Methyl α-bromopropionate was prepared in 73% yield by Walker's method (*J.*, 1895, **67**, 922). The bromopropionate (70 g.) and potassium fluoride (35 g.) were heated in a rotating autoclave at 200—210° for 7 hours. The mixture was then extracted with ether, filtered, the ether distilled off, and the residue fractionated. The following fractions were obtained: (*a*) 100—120°, (*b*) 120—140° (steady rise to small amount of unchanged bromo-ester). The first fraction on redistillation gave *methyl α-fluoropropionate*, b. p. 106·5—108·5° (Found: C, 45·6; H, 6·9; F, 18·0. $C_4H_7O_2F$ requires C, 45·3; H, 6·6; F, 17·9%).

Methyl α-Bromoisobutyrate.—Red phosphorus (12·5 g., 0·4 mol., dried over phosphoric oxide) and *iso*butyric acid (70·4 g., 0·8 mol.) were mixed, and bromine (319·6 g., 4 mols., dried over concentrated sulphuric acid) was added slowly. After the addition was complete, the mixture was heated under reflux on the water-bath for 5 hours. The water condenser was then replaced by a calcium chloride tube, and the mixture heated for another hour. It was then cooled and carefully mixed with methyl alcohol (128 g., 4 mols.). After addition to a saturated solution of sodium carbonate cooled in ice–salt, a heavy oil separated. The aqueous layer was extracted with ether, and the extract added to the oil. The mixture was washed in turn with 10% aqueous sodium bisulphite, aqueous sodium carbonate, and water, and then dried (Na_2SO_4). After removal of the ether the residual liquid came over almost entirely at 53—55°/21 mm.; yield 121·9 g. (84·2%).

Methyl α-Fluoroisobutyrate.—A mixture of methyl α-bromo*iso*butyrate (72·4 g., 0·4 mol.) and dry silver fluoride (76·2 g., 0·6 mol.) was refluxed, with stirring, for 3 hours. It was then cooled, and the solid filtered off. The solid was washed with ether, which on being added to the filtrate, precipitated more solid, necessitating further filtration. After drying (Na_2SO_4), the ether was distilled off, and more solid filtered off. The distillate of b. p. 24—30°/24 mm. was collected and redistilled at ordinary pressure; b. p. 108—109°. After a further distillation, the fraction of b. p. 108—109° was collected, but was still probably not quite pure. The *ester* contained fluorine (Found: C, 52·0; H, 7·5. $C_5H_9O_2F$ requires C, 50·0; H, 7·52%).

Ethyl 1:3-*Difluoroacetoacetate.*—(a) *Condensation using sodium in presence of methyl alcohol.* MFA (75 g.) and methanol (2 c.c.) were placed in a flask and sodium wire (7·5 g.) was added. The reaction began immediately and was complete within 30 minutes. It was necessary to control the reaction by cooling in ice–water. After all the sodium had reacted, a mobile liquid remained which was acidified with glacial acetic acid and then diluted with water to *ca.* 300 c.c. The liquid was extracted with ether, the extract dried (Na_2SO_4), and the ether distilled off. The residue was fractionally distilled, and the *difluoroacetoacetate* collected at 97°/14 mm.; yield 14 g. (23%). MFA recovered, 25 g.; overall yield of the difluoroacetoacetate, 35% (Found: C, 39·3; H, 4·06; F, 24·9, 24·84. $C_5H_6O_3F_2$ requires C, 39·5; H, 4·95; F, 25·0%).

(b) *Condensation using sodium.* Sodium wire (7·5 g.) was added to freshly distilled MFA (75 g.). The reaction began after 5—40 minutes and was moderated initially by cooling in ice. When no more sodium remained (*ca.* 100 minutes) the dark brown semi-solid mass was dissolved in water (300 c.c.), acidified with glacial acetic acid (5 c.c.), and extracted three times with a total of 250 c.c. of ether. The extract was dried (Na_2SO_4), and after the ether had been distilled off, the resulting liquid was fractionated under reduced pressure. Two fractions were obtained: (1) b. p. 30—35°/20 mm. (recovered MFA); (2) b. p. 103—105°/20 mm. (mainly difluoroacetoacetate). Fraction (1) was redistilled, giving MFA (25 g.) b. p. 103—105°/760 mm.; (2) was redistilled, giving the acetoacetate (9 g., 15%), b. p. 104°/20 mm. Yield of ester allowing for recovered MFA, 22·5%.

Notes. (i) Unless all the dark brown semi-solid was dissolved in water, the yield was reduced. (ii) The MFA in fraction (1) usually contained acetic acid which was removed by shaking with the minimum amount of saturated sodium carbonate solution. If excess of sodium carbonate was used some MFA was lost.

(c) *Condensation using sodium methoxide.* Sodium methoxide (20 g.) was added slowly to MFA (70 g.), and the mixture heated under reflux for 6 hours in an oil-bath. (The addition of MFA to the methoxide caused charring.) The resulting mixture was acidified, extracted with ether, the ether extract dried (Na_2SO_4), and the residue distilled. No appreciable quantity of difluoroacetoacetic ester was obtained.

Fluoroacetic Acid.—A few drops of phenolphthalein solution were added to a mixture of methyl fluoroacetate (46·0 g., 0·5 mol.) and water (100 c.c.) and then powdered barium hydroxide octahydrate (78·9 g., 0·25 mol.) was added in small portions, the mixture being mechanically stirred after each addition until the alkaline reaction had disappeared. The resultant liquid was then made acid, if necessary, by the addition of a few drops of methyl fluoroacetate, filtered, and the filtrate concentrated to about 100 c.c. on a water-bath. The liquid was cooled, and methylated spirit (500 c.c.) added in order to precipitate the barium fluoroacetate, which was filtered off, drained, and dried, but not recrystallised; yield 69·0 g. (95·0%).

Dry barium fluoroacetate (58 g., 0·2 mol.) was slowly added to 100% sulphuric acid (122·5 g., 1·25 mols.). On distillation under reduced pressure, using a wide air-condenser, the fluoroacetic acid came over between 83° and 100°/17 mm. and crystallised immediately. It was redistilled at atmospheric pressure and came over at 167—168·5°; yield 29·5 g. (94·2%); colourless needles, m. p. 31—32° (Found: F, 24·3. Calc. for $C_2H_3O_2F$: F, 24·4%). These yields are considerably higher than those obtainable by Swarts's original method (*loc. cit.*).

Fluoroacetyl Chloride.—Phosphorus pentachloride (93·8., 0·45 mol.) was placed in a 250-c.c. round-bottomed flask and cooled in ice–water. The flask was fitted with a reflux condenser and an inlet tube connected to a flask which could be rotated to allow the just molten fluoroacetic acid (31·2 g., 0·4 mol.) to be added in small quantities. At first the reaction was vigorous, but later, external cooling could be discontinued. After the addition was completed, the mixture was heated under reflux for

45 mins. in an oil-bath at 100°. The liquid was then distilled through a 30-cm. fractionating column, and the fraction of b. p. 72—80° collected. On redistillation, most of it came over at 71·5—73°/760 mm.; yield, 27 g. *Fluoroacetyl chloride* is a liquid with a pungent odour and is readily hydrolysed by water (Found: F, 19·7. C_2H_2OClF requires F, 19·7%).

Chloroacetyl Fluoride.—(*a*) A mixture of chloroacetyl chloride (113 g.) and dry potassium fluoride (69·6 g., 1·2 mols.) was heated for various times at various temperatures (see below) in a rotating autoclave. A slight pressure always remained in the apparatus at the end of the experiment, and the material was always charred, but excessive decomposition did not take place. The solid was extracted with xylene and fractionated, the fraction of b. p. 70—90° being collected and refractionated (Found: F, 19·6. Calc. for C_2H_2OClF: F, 19·7%).

200° for 45 mins.	Yield 32·0 g. (33·2%).	B. p. 73—75°/760 mm.	
200° ,, 20 ,,	,, 43·7 g. (45·2%).	,, 73—76/	,,
170° ,, 30 ,,	,, 53·7 g. (55·6%).	,, 73—76/	,,

(*b*) By heating chloroacetyl chloride under reflux with potassium fluoride in nitrobenzene for 6 hours a 6·8% yield of chloroacetyl fluoride was obtained.

(*c*) By heating chloroacetyl chloride, potassium fluoride, and benzoyl chloride at about 150° for 1 hour, a 15·8% yield of chloroacetyl fluoride was obtained. The compound had been prepared by Traube and Krahmer (*Ber.*, 1919, **52**, 1079) in 15% yield by the action of fluorosulphonic acid on chloroacetic acid.

Fluoroacetyl Fluoride.—(*a*) A mixture of fluoroacetic acid (23·4 g., 0·3 mol.) and dry potassium fluoride (23·2 g., 0·4 mol.) was placed in a flask fitted with dropping-funnel and reflux condenser through which water at 60° was passing. Fitted to the top of this condenser was a thermometer in a still-head which led to a long water-condenser and a trap, closed by a calcium chloride tube and cooled in an ice–salt mixture. The mixture in the flask was gently heated and stirred while benzoyl chloride (42·2 g., 0·3 mol.) was added from the dropping-funnel during 40 mins. Fuming and charring occurred and a small quantity of liquid collected in the trap, the thermometer in the still-head registering 32—40°. After all the benzoyl chloride had been added, the mixture was heated for a few minutes, but no more liquid distilled over and the benzoic acid present began to sublime. The *fluoride* collected was redistilled and had b. p. 50·5—51°; yield 4·1 g. (17·1%) (Found: F, 48·2. $C_2H_2OF_2$ requires F, 47·5%). It was advantageous to have a solvent (*e.g.*, nitrobenzene) present in the original mixture to facilitate mixing.

(*b*) A mixture of fluoroacetyl chloride (19·3 g., 0·2 mol.) and dry, powdered antimony trifluoride (17 g., 0·1 mol.) was heated gently under reflux for 3 hours. Some fuming occurred during this heating. The mixture was then cooled, the residual solid filtered off, and the filtrate distilled. A fraction was collected between 44° and 51° (mostly 50—51°) and a higher-boiling chloride was left behind; yield of product 10·3 g. (64·4%). On redistillation, the liquid had b. p. 50·5—51°, and was proved to be fluoroacetyl fluoride.

Ethyl Fluoroformate.—A mixture of ethyl chloroformate (108·5 g., 1 mol.) and dry potassium fluoride (69·6 g., 1·2 mols.) was heated in a rotating autoclave for 3 hours at 100—105°. After cooling, a pressure of 5 atm. still remained. The product was extracted with pure dry xylene and filtered. The filtrate was carefully fractionated using an 80-cm. column. Two fractions (*a*) and (*b*) were collected before the xylene started to come over: (*a*) b. p. 40—60°, 26 g.; (*b*) b. p. 60—105°, mainly unchanged chloroformate. The fraction (*a*) was twice redistilled, and *ethyl fluoroformate* of b. p. 55·5° was collected. This fraction was chlorine-free, and reacted vigorously with aqueous ammonia (Found: F, by refluxing with sodium in alcohol, 20·4, 20·8. $C_3H_5O_2F$ requires F, 20·65%).

Action of Paraformaldehyde on Fluoroacetyl Fluoride.—This was an attempt to obtaine fluoromethyl fluoroacetate. It seemed that none of this compound was formed but methylene bisfluoroacetate was isolated. Descudé (*Compt. rend.*, 1903, **136**, 1566) obtained some of the chloro-analogue together with some chloromethyl chloroacetate in the corresponding reaction with chloroacetyl chloride.

A mixture of paraformaldehyde (3·6 g., 0·12 mol.) and fluoroacetyl fluoride (9·6 g., 0·12 mol.), together with a few pieces of zinc chloride, was heated on the water-bath until the solid disappeared (about 3 hours). After cooling, the liquid was transferred to a distilling flask. At the beginning of distillation, it seemed that some gaseous decomposition products were being evolved. As the temperature rose, distillate began to come over and solidified on cooling. Distillation was continued up to 180°/15 mm., and the solid material thus obtained was recrystallised from light petroleum (b. p. 40—60°), it being found advantageous to use a continuous extraction apparatus owing to the low solubility of the product in this solvent. With benzene, the substance became deep purple during attempted recrystallisation. The *methylene bisfluoroacetate* consisted of small colourless needles, m. p. 57° (Found: F, 22·9. $C_5H_6O_4F_2$ requires F, 22·6%).

Sodium Fluoroacetate.—To methyl fluoroacetate (46·0 g., 0·5 mol.) suspended in water (100 c.c. containing a few drops of phenolphthalein), sodium hydroxide (0·5 mol., 20 g. in 100 c.c. water) was added slowly. The mixture was kept well stirred, and the rate of addition governed by the disappearance of the red coloration. When the addition of sodium hydroxide was complete, a few more drops of MFA were added to render the solution acid. It was then evaporated on the water-bath until crystallisation started, cooled, and the solid filtered off. More solid was obtained from the filtrate by the addition of alcohol; total yield 45·5 g. (91·0%) (Found: F, 19·0. Calc. for $C_2H_2O_2FNa$: F, 19·0%). This was characterised as *p-nitrobenzyl fluoroacetate* as follows. *p*-Nitrobenzyl bromide (0·9 g.), dissolved in alcohol (10 c.c.), was added to a solution of sodium fluoroacetate (0·3 g.) in the minimum amount of water. The mixture was heated under a reflux condenser for 2 hours and allowed to cool; the solid was collected by filtration, and crystallised from ethanol as long needles, m. p. 76° (Found: C, 50·9; H, 4·10; N, 6·7. $C_9H_8O_4NF$ requires C, 50·7; H, 3·8; N, 6·6%).

Fluoroacetic Anhydride.—Sodium fluoroacetate (15 g., 0·15 mol., dried in a vacuum over sulphuric acid) was placed in a Claisen flask, and fluoroacetyl chloride (12·1 g., 0·125 mol.) added slowly from a dropping-funnel; the heat developed was small. The mixture was then refluxed in an oil-bath at 110—120° for 1½ hours. The contents were distilled under reduced pressure, and initially the distillate

was collected in one fraction. This started to come over at 108°/41 mm. but when the temperature reached 110° the pressure began to fall, and finally a b. p. of 106° 32 mm. was recorded; yield 13·4 g. (77·7%). On redistillation, most of the liquid came over at 88—89°/12 mm. The *anhydride* was found to be chlorine-free (Found: F, 28·0. $C_4H_4O_3F_2$ requires F, 27·52%).

Triethyl-lead Fluoroacetate.—To fluoroacetic acid (2·3 g., 0·03 mol.) dissolved in absolute ether (5 c.c.) were added tetraethyl-lead (9·7 g., 0·03 mol.) and a few pieces of silica gel. After 5 mins. warming on a water-bath, a white solid began to crystallise out, and at the end of 15 mins. the mixture was almost solid. After standing at room temperature for a few hours, the white crystals (almost pure) were drained thoroughly at the filter-pump; yield, 8·8 g. (79·1%). Recrystallised from toluene containing a small quantity of ethyl alcohol, *triethyl-lead fluoroacetate* had m. p. 180·5° (decomp.) (Found: Pb, 55·5. $C_8H_{17}O_2FPb$ requires Pb, 55·8%). A slight yellow coloration developed at about 165°, but this disappeared before melting occurred.

Glycol Bisfluoroacetate.—Freshly distilled glycol (b. p. 194°, 5 g.) was placed in a small Claisen flask fitted with a water-condenser and a dropping-funnel in the two vertical arms, the side arm being closed. Fluoroacetyl chloride (16 g.) was added slowly from the dropping-funnel, the flask being kept cool. The product was then heated to 100° (oil-bath) and then distilled, two fractions being obtained; the first had b. p. 85—90°/22 mm. (unchanged glycol, 3 g.), and the second had b. p. 140—141°/11 mm. and was the required *ester* (5·3 g.) (Found: F, 21·1. $C_6H_8O_4F_2$ requires F, 20·9%). The compound is a stable, viscous, colourless liquid, insoluble in water, soluble in the usual organic solvents.

Cholesteryl Fluoroacetate.—Fluoroacetyl chloride (10 g.) was added to cholesterol (5 g.), and the mixture heated under reflux on a water-bath for 1 hour. The cholesterol dissolved and the solution developed a blue and then a red-brown coloration. After cooling, a mixture of water (25 c.c.) and alcohol (25 c.c.) was added to precipitate the product and to hydrolyse unchanged fluoroacetyl chloride (cooling required). The solid was then filtered off, washed well with water to remove fluoroacetic acid, and the *cholesteryl fluoroacetate* was recrystallised from ethyl alcohol; yield, (3·7 g., 62%), m. p. 144—144·5°. The condensation was also carried out in the presence of pyridine, and an identical product was obtained, m. p. 144·5°; mixed m. p. with cholesterol (m. p. 148°), 120—130°. The compound was insoluble in water or cold alcohol, readily soluble in chloroform, and more readily soluble than cholesterol in cold acetone. It was found to be chlorine-free (Found: F, 3·98, 4·10. $C_{29}H_{45}O_2F$ requires F, 4·17%). Hydrolysis with 0·1N-alcoholic soda showed it to contain one fluoroacetyl group; the product of hydrolysis had m. p. 146·5° and did not contain fluorine: it was therefore cholesterol.

O-(*Fluoroacetyl*)*salicylic Acid.*—Salicylic acid (10 g.) was dissolved in pyridine (7 c.c.) and then fluoroacetyl chloride (9·6 c.c.) was added in small portions, a considerable amount of heat being evolved. The product was heated on a boiling water-bath for 7 minutes, and then slowly poured into cold water (300 c.c.). The heavy oil which separated crystallised after vigorous stirring and scratching for 20 minutes (11 g., 85%). After being thoroughly dried in a desiccator it was recrystallised twice from benzene; m. p. 131·6 (5·3 g., 40%) (Found: F, 9·76. $C_9H_7O_4F$ requires F, 9·5%). The *acid* was slightly soluble in cold water, readily soluble in hot water and in cold dilute sodium hydroxide solution. It gave no coloration with ferric chloride (absence of phenolic hydroxyl group).

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359. *Structure of Acorn Starch.*

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The proportion (3%) of terminal to non-terminal glucose residues in acorn starch has been determined by four different methods which give concordant results. This starch contains 80% of amylopectin, and it follows that in the amylopectin component there are 24 glucose residues per terminal group. The special features of the acetyl and methyl derivatives of acorn starch are their high viscosities in *m*-cresol and their high molecular weights. A colorimetric method is described for the determination of methylated amylose in the presence of methylated amylopectin. The periodate oxidation procedure has been extended to provide evidence of the mode of attachment of the side chains in amylopectin, and it is shown that at least 75% of these are linked to the main chain at C_6 of one of the glucose residues in the latter.

THE proportion of non-terminal to terminal glucose residues has already been determined for many starches, the values obtained both by the methylation procedure and by the periodate oxidation method (cf. Brown, Dunstan, Halsall, Hirst, and Jones, *Nature*, 1945, **156**, 785) varying for the whole starches between 20 and 30 glucose units per end group, according to the type of starch under examination. Since methods are now available for determining the proportion of amylose present in any starch, it is possible to calculate the proportion of non-terminal to terminal residues in the amylopectin component even where complete separation of the two components is difficult or impossible. For most starches this ratio is about 20 to 1, but for some amylopectins a slightly higher ratio of 24 to 1 has been observed. In the present paper these investigations have been extended to the starch from the acorn of the oak-tree (*Quercus*

robur, Linn.). The starch was separated from the macerated cotyledons by the sulphite process, and the properties of both the acetate and the fully methylated derivatives were studied. It was found that both these derivatives possess initial high specific viscosities in *m*-cresol, and although the values lie so much beyond the range of permissible extrapolation from the figures recorded for the relationship between the viscosity and molecular weight of starch derivatives (Hirst and Young, *J.*, 1939, 1471) it is clear that the amylopectin of acorn starch must have an extremely high molecular weight. In this connection it may be significant that the ordinary method for the separation of the amylose and the amylopectin components (cf. maize starch, Higginbotham and Morrison, *Chem. and Ind.*, 1947, 45) was unsatisfactory, only slight separation being effected. At present, however, there is insufficient evidence to decide whether this difficulty is due to some kind of association between the two components or to physical protection of the amylose by the highly colloidal amylopectin.

It has been found in connection with other investigations that with suitable concentration of the reagents fully methylated amyloses gave a blue colour with iodine whilst methylated amylopectins under the same conditions gave no appreciable colour. It is possible, therefore, by modification of the method of Hassid and McCready (*J. Amer. Chem. Soc.*, 1943, **65**, 1154) to determine by means of the blue value the proportions of methylated amylose and amylopectin in a methylated starch. Such determinations were used in the present work as a test of the separation of the methylated amylose and methylated amylopectin in the course of fractionating experiments. These were carried out by extracting methylated acorn starch with mixtures of ether and acetone, but, as happened also with the original starch, no appreciable separation of the constituents could be effected, the blue value being approximately the same for all fractions. A similar failure was recorded when attempts were made to fractionate methylated acorn starch by passing a solution of it in a mixture of benzene and light petroleum through a column of alumina. All the fractions recovered gave blue colours with iodine, but the blue value of the first (0·47) was slightly lower than that of the original methylated starch (0·57), indicating that some slight degree of separation had been achieved.

The proportion of terminal groups in acorn starch was estimated by the following methods:

(*a*) Determination of the tetramethyl methylglucoside content on methanolysis of the methylated derivative by partition between water and light petroleum (Brown and Jones, *J.*, 1947, 1344).

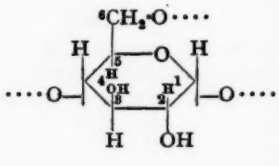
(*b*) Determination of the tetramethyl methylglucoside by chromatography on alumina (Jones, *J.*, 1944, **33**; Brown and Jones, *loc. cit.*).

(*c*) Fractional distillation of the tetramethyl methylglucoside (Hirst and Young, *J.*, 1938, 1247).

(*d*) The periodate oxidation method on the unmethylated starch (Brown, Dunstan, Halsall, Hirst, and Jones, *loc. cit.*).

By these methods it was found that the proportion of non-terminal to terminal glucose residues was approximately 30 to 1 in the whole starch, and since the amylose content was 20%, as determined by the iodine potentiometric method, it follows that the proportion of non-terminal to terminal sugar residues in the amylopectin component of acorn starch was approximately 24 to 1. Acorn starch is, therefore, essentially similar in this respect to the many other starches for which figures have been published.

Notwithstanding its high molecular weight, the amylopectin of acorn starch contains one terminal glucose residue for every 24 non-terminal glucose units, and it is clear, therefore, that the molecule of the amylopectin must have a branched-chain structure. There is some evidence that in other starches the branching occurs through C_6 of one of the 1 : 4 α-linked glucose residues in the main chain (Freudenberg and Boppel, *Ber.*, 1940, **73**, 609; Barker, Hirst, and Young, *Nature*, 1940, **147**, 296). The evidence from which these conclusions are drawn is based on the identification of 2 : 3-dimethyl glucose amongst the hydrolysis products of fully methylated starch. In the course of the present investigation another method of approach to this problem was attempted by means of an extension of the periodate oxidation method. If branching occurs through C_6 (inset formula) of any particular glucose residue, the juxtaposed hydroxyl groups on C_2 and C_3 of this residue remain unsubstituted. Attack with periodate would therefore disrupt the glucose residue, and, if all the branchings occur through C_6, oxidation of the amylopectin by periodate would yield a product which on subsequent hydrolysis would give no free glucose. On the other hand, if branching occurs through C_2 or C_3 the glucose residue in question contains no α-glycol grouping and would not be disrupted by periodate. The final hydrolysis product obtained from



the oxidised starch would in this case contain free glucose. In carrying out this method of attack experimental difficulties were encountered in the identification and determination of small quantities of glucose admixed with a large excess of oxidation products. It was found, however, that the chromatographic technique of Partridge (*Nature*, 1946, **158**, 270) could be used effectively to solve the problem, and for quantitative work the chromatographic procedure developed by Flood, Hirst, and Jones (*Nature*, 1947, **160**, 86) was found to be effective. The results showed that, with acorn starch as also with potato starch, a very small proportion of glucose (less than 1·3% of the weight of starch) was found after oxidation by periodate and subsequent hydrolysis. The significance of this small yield of glucose is difficult to assess at the moment, and we defer for later consideration the question whether this is of structural importance or is due to incomplete attack by the periodate. The proportion of glucose residues remaining unoxidised is very similar to the proportion of glucose residues involved in the disaggregation process when methylated amylopectin is subjected to the mild hydrolytic action of methyl alcoholic oxalic acid (Hirst and Young, *J.*, 1939, 1471): what is abundantly clear, however, is that by far the greater proportion of the side chains, at least 75%, must be attached to the main chains through the 1 : 6 linkages.

Experimental.

Preparation of Starch.—The outer husks were removed from freshly collected acorns (1 kg.), and the cotyledons soaked for 7 days in water containing sulphur dioxide. The skins were then removed and the cotyledons passed through a mincing machine. The resultant slurry was rubbed through linen, and the starch allowed to separate out. The crude material was washed by decantation and freed from fibrous matter by allowing it to settle. The first material to separate was mainly fibre, and this was followed by a deposit of practically pure starch.

The product (*ca.* 70 g.) was purified by extraction with aqueous dioxan to remove fats. The light grey powder was examined under the microscope, and the granules were seen to be of a very different shape and dimension from those of potato starch, being much smaller and the hilum not being eccentric as it is in potato starch. Only a very small amount of broken-down thin cell-wall membrane could be seen admixed with the starch. The starch gave with boiling water a grey paste which was much more viscous than that given by potato starch under the same conditions. It was completely soluble in N-sodium hydroxide. On addition of the sodium hydroxide solution the starch turned deep brown, and by gentle warming it gave a yellow solution. A dispersion of the starch in water gave a deep blue coloration with iodine. The blue value at 20°, determined by the method of Hassid and McCready, was 0·42—0·44 (potato starch under similar conditions gave a blue value of 0·47). On hydrolysis for 7 hours with boiling 2% sulphuric acid (250 parts), the starch (1 part) gave 95% of the theoretical amount of glucose. (Two similar determinations with pure potato starch gave 98·7% of the theoretical amount.) No visible residue was left after hydrolysis. Fehling's test, negative; $[\alpha]_D^{16°}$ + 168° (*c*, 0·33 in N-sodium hydroxide) [Found, on a dried sample: sulphated ash, 0·5; furfuraldehyde (on boiling with 12% hydrochloric acid), 0·8%; glucose under these conditions yields 0·6% of furfuraldehyde].

Separation of Amylose.—Schoch's butanol method (*loc. cit.*) gave only a very incomplete separation of amylose on the material defatted by extraction with a mixture of dioxan and water. The amylose fraction had a blue value of 0·61 only, indicating, however, that some concentration of amylose had occurred; this value was higher than that of the initial starch (0·43) but considerably lower than that of pure amylose (about 1·40). Repetition of the process resulted in little further separation of the components.

Potentiometric Determination of Amylose.—The method used was the modification elaborated by Wilson, Schoch, and Hudson (*J. Amer. Chem. Soc.*, 1943, **65**, 1381) of the method of Bates, Rundle, and French (*ibid.*, p. 142). The amount of iodine taken up by 1 g. of starch was 0·0425 g. If 21·5% is the amount of iodine taken up by pure amylose (Higginbotham and Morrison, *Chem. and Ind.*, 1947, 45), the amylose content of the sample of acorn starch was 19·8%.

Acetylation of Acorn Starch.—The starch was acetylated in a similar manner to that described by Hirst and Young (*J.*, 1939, 953) for wheat starch. The air-dried starch (12 g.) was made into a paste (3%) with hot water (400 c.c.). The paste was grey and very viscous. It was precipitated by pouring it into methylated spirit (2000 c.c.). After filtration, the product was washed thrice with methylated spirit and dried under reduced pressure over calcium chloride, and a snow-white fluffy material (11 g.) thus obtained. This was mixed with pyridine (110 c.c.) and the mixture stirred for 7 hours and kept overnight (16 hours) at room temperature (10°). It gave a transparent homogeneous jelly. Acetic anhydride (110 c.c.) was then added, and the mixture stirred for a further 45 hours at 60° and 154 hours at 10°. The viscous, light brown, homogeneous solution was diluted with glacial acetic acid (350 c.c. and poured into ice-cold water. The acetate was washed with water until free from acid, then with alcohol and ether, and dried in a vacuum over calcium chloride. Yield, 17·5 g. (90% of the theoretical); $\eta_{sp.}^{30°}/c$ 2·57 (*c*, 0·54 in *m*-cresol) (Found: $CH_3{\cdot}CO$, 45·3%). This acetate was almost entirely soluble in acetone, and the solution gave on evaporation a milky and fragile film.

Acorn starch was much more difficult to acetylate than potato starch. A comparative experiment with the latter gave a homogeneous and much more fluid solution after only 2 hours' stirring at 25°.

Direct Methylation of Granular Acorn Starch.—The granular acorn starch was methylated under conditions similar to those used by Hirst and Young (*loc. cit.*) for rice starch. Starch (18·2 g.) was made into a cream with cold water (150 c.c.), and 30% sodium hydroxide (100 c.c.) was added. The gel was dispersed by addition of water (50 c.c.); 30% sodium hydroxide (400 c.c.) and methyl sulphate (200 c.c.) were then added gradually at room temperature with vigorous mechanical stirring. After 15 hours' stirring at room temperature the alkali was partly neutralised with 50% sulphuric acid (120 g.). The

solution was evaporated on the steam-bath, and the product (without separation of mineral salts) was remethylated with methyl sulphate (135 c.c.) and 30% sodium hydroxide (330 c.c.). After 15 hours' stirring at room temperature, acetone (500 c.c.) was added and the mixture was evaporated on the steam-bath. The insoluble methylated starch was removed from the surface of the mixture, dissolved in acetone (400 c.c.) and water (100 c.c.), and remethylated with methyl sulphate (140 c.c.) and 30% sodium hydroxide (350 c.c.). After this methylation procedure had been repeated a further 7 times the product was purified by dissolution in aqueous acetone followed by filtration and removal of the solvent by distillation. It was dried under reduced pressure and extracted with ether in a Soxhlet apparatus. Yield, 18·4 g. (78% of the theoretical) (Found : OMe, 42·6%).

Fractionation of the Methylated Starch.—The methylated starch (16·7 g.) was extracted successively by boiling it for 4 hours under reflux with mixtures of ether and acetone, 80 : 20, 60 : 40, 20 : 80, and 100% by volume respectively. The blue values of the fractions were determined in the following way (cf. Hassid and McCready, *loc. cit.*). The methylated starch (25 mg.) was dissolved in cold water (25 c.c.). The solution (5 c.c.) was mixed with iodine reagent (5 c.c.) (Hassid and McCready, *loc. cit.*) and diluted to 100 c.c. The intensity of the colour recorded as log I/I_0 was measured at 20° in a Spekker absorptionmeter using 1 cm. cells and a red filter. On dilution to 300 c.c. the blue colour disappeared completely and suddenly. (1) 0·37 G.; $[\alpha]_D^{16°}$ + 208° (*c*, 0·37 in acetone); $\eta_{sp.}^{20°}/c$ 0·248 (*c*, 0·46 in *m*-cresol), corresponding to an apparent *M* of 55,000 (see Hirst and Young, *J.*, 1939, 1475); OMe, 43·6%. (2) 10·7 G.; $[\alpha]_D^{15°}$ + 209° (*c*, 0·38 in chloroform); B.V. 0·57; $\eta_{sp.}^{20°}/c$ 1·97 (*c*, 0·41 in *m*-cresol), corresponding to an apparent *M* of 725,000; OMe, 43·8%. (3) 3·85 G.; $[\alpha]_D^{15°}$ + 209° (*c*, 0·68 in chloroform); B.V. 0·56; $\eta_{sp.}^{20°}/c$ 1·93 (*c*, 0·38 in *m*-cresol), corresponding to an apparent *M* of 750,000; OMe, 43·8%. (4) 1·4 G.; $[\alpha]_D^{15°}$ + 209° (*c*, 0·75 in chloroform); B.V. 0·61; $\eta_{sp.}^{20°}/c$ 2·28 (*c*, 0·45 in *m*-cresol), corresponding to an apparent *M* of 770,000; OMe, 43·1%. (5) 0·10 G.; $[\alpha]_D^{15°}$ + 209° (*c*, 0·43 in chloroform); B.V. 0·35; OMe, 38·7%. (6) A residue insoluble in acetone, 0·06 g.; this gave no blue colour with iodine. The losses during fractionation were 0·18 g. or 1·1%.

Determination of End-groups.—Three different methods were used to determine the proportion of tetramethyl methylglucoside present in the products obtained on methanolysis of the methylated starch, namely, distillation, partition between light petroleum and water, and chromatography on alumina. The methanolysis was effected by boiling the methylated starch (1 part) with 1% methyl-alcoholic hydrogen chloride (50 parts) for 7 hours. The solution was then removed by addition of an ethereal solution of diazomethane and finally concentrated to a syrup on the boiling water-bath.

(a) *Distillation method.* A sample of methylated starch (fraction 2, 2·52 g.) was boiled with methyl-alcoholic hydrogen chloride, and the resultant methylglucosides isolated as described above. The syrup (2·7 g.) was dissolved in water (50 c.c.) and extracted with light petroleum (b. p. 40—50°, specially purified) in an all-glass continuous extractor. After extraction (30 hours) the solvent was distilled off and the residual syrup (0·952 g.) was distilled under reduced pressure (1·0 mm.). Two fractions were collected: (i) (bath temp. *ca.* 135°) 0·197 g.; $n_D^{20°}$ 1·4484; $[\alpha]_D^{16°}$ + 14·8° (*c*, 1·55 in water). (ii) (bath temp. 135—145°) 0·116 g.; $n_D^{19°}$ 1·4555; $[\alpha]_D^{15°}$ + 11·8° (*c*, 1·17 in water). Fraction (ii) was pure trimethyl methylglucoside (cf. Hirst and Young, *loc. cit.*). The proportion of tetramethyl methylglucoside in the first fraction was 46%; 10% was added for losses, giving a total amount of 0·10 g. of tetramethyl methylglucoside from 2·520 g. of initial methylated starch. The ratio of non-terminal to terminal groups calculated from these figures was 29 : 1.

(b) *Partition method* (Brown and Jones, *loc. cit.*). The methylated starch (fraction 2, 2·574 g.) was boiled with 1% methyl-alcoholic hydrogen chloride, and hydrogen chloride was then removed by addition of diazomethane. The syrupy glucosides (2·9 g.) isolated on concentration of the neutral solution were dissolved in water (50 c.c.), and the solution poured into the upper part of a double continuous all-glass extractor. In the lower part of the extractor water (50 c.c.) was introduced. The following fractions were obtained by successive extractions of 7 hours with light petroleum (b. p. 40—60°; free from sulphur compounds and unsaturated paraffins). Fraction 1, 0·220 g.; $n_D^{22°}$ 1·4490. Fraction 2, $n_D^{22°}$ 1·4490. Fraction 3, $n_D^{22°}$ 1·4500. Fraction 4, 0·056 g.; $n_D^{22°}$ 1·452. Fraction 5, 0·116 g.; $n_D^{20°}$ 1·455. The last fraction crystallised and was pure trimethyl methylglucoside. The first 4 fractions were combined and extracted in the same way, and the following fractions were then isolated: (*a*) 0·110 G.; $n_D^{22°}$ 1·4452. (*b*) 0·019 G.; $n_D^{22°}$ 1·4503; $[\alpha]_D^{21°}$ + 21° in water. (*c*) 0·024 G.; $n_D^{18°}$ 1·4553. This fraction crystallised and was pure trimethyl methylglucoside. Fraction (*a*), a pale yellow liquid, was distilled in a micro-distillation apparatus, and gave a colourless distillate (102 mg.; $n_D^{24°}$ 1·4430; $[\alpha]_D^{24°}$ + 31° in water) and a brown residue (7·4 mg.). As the distillate was not pure tetramethyl methylglucoside it was distilled in the same apparatus and gave three fractions: (*α*) 64 Mg.; $n_D^{18°}$ 1·4427; $[\alpha]_D^{19°}$ + 45° in water) (Found : OMe, 60·3%). (*β*) 30·7 Mg.; $n_D^{19°}$ 1·4480 (Found: OMe, 55·2%). (*γ*) A brown residue, 3·5 mg. (Found : OMe, 45%). Fraction (*a*) is pure tetramethyl methylglucoside. From the values of refractive indices and specific rotations it was calculated that fraction (*β*) contained 56% or 17·3 mg. of tetramethyl-glucoside and fraction (*b*) 32% or 6·0 mg. of tetramethyl methylglucoside. The total amount of tetramethyl methylglucoside was then 88 mg; 10% was added to this figure for losses during extraction and distillation. The ratio of non-terminal to terminal groups calculated from this figure was 30 : 1.

(c) *Alumina chromatogram method* (Brown and Jones, *loc. cit.*). The methylated starch (4·64 g., fraction 2) was boiled with 1% methyl-alcoholic hydrogen chloride, and the hydrogen chloride was removed by addition of ethereal diazomethane. The syrupy methylglycosides obtained by removal of the solvent were dissolved in water (50 c.c.), and the solution was extracted continuously with light petroleum (b. p. 40—60°, specially purified) until all the tetramethyl methylglucoside had been removed, i.*e.*, until a sample of the petroleum on evaporation left a syrup which had a refractive index corresponding to that of trimethyl methylglucoside. The mixture of methylglucosides (*ca.* 0·3 g.) was dissolved in light petroleum (50 c.c., b. p. 40°, purified) and passed through a column of activated alumina (British Aluminium Co., Burntisland) and eluted with dry alcohol-free chloroform. The following fractions were obtained. (A) 156 Mg.; $n_D^{21°}$ 1·4420; $[\alpha]_D^{19°}$ + 63·5° (*c*, 1·56 in water). (B) 78 Mg.; $n_D^{19°}$ 1·4502; $[\alpha]_D^{20°}$ + 32° (*c*, 3·41 in water). (C) 28 Mg.; $n_D^{20°}$ 1·4550; $[\alpha]_D^{19°}$ + 18·6° (*c*, 1·1 in water). Fraction (A)

is pure tetramethyl methylglucoside, (C) is pure trimethyl methylglucoside, and (B) is a mixture of the two containing 40% or 31·2 mg. of tetramethyl methylglucoside. The total yield of tetramethyl methylglucoside is 187 mg., corresponding to the occurrence of one end group in every 30 glucose residues.

Determination of End Group in Acorn Starch by the Periodate Oxidation Method.—A sample of starch (0·50 g.) was dissolved in water (80 c.c.) containing potassium chloride (5 g.) and oxidised with sodium metaperiodate (40 c.c., 0·31M). The mixture was shaken, and at intervals samples (20 c.c.) were withdrawn, ethylene glycol added to destroy the excess of periodate, and the formic acid titrated, using methyl-red as indicator (Found: G.-mol. of formic acid per 162 g. starch: 7 days, 0·035; 8 days, 0·036; 10 days, 0·036). The percentage of end group calculated from the yield of formic acid after 7 days was 29.

Determination of Glucose Residues Linked through C_1, C_4, *and* C_6.—The starch (2 g.) was mixed with 0·27M-sodium periodate (60 c.c.), potassium chloride (10 g.), and water (220 c.c.) in a 500 c.c. glass-stoppered bottle, and the mixture was shaken for 10 days at room temperature. Excess of ethylene glycol (5 c.c.) was then added, and shaking was continued for 24 hours. The oxidised starch was filtered on a G3 sintered-glass filter, washed with cold water until free from oxidant (test with potassium iodide and sulphuric acid and diphenylamine and sulphuric acid) and then with alcohol, and dried in a vacuum desiccator over calcium chloride. The dry oxidised starch was hydrolysed with N/2-sulphuric acid (200 c.c.) for 10 hours at 95°. To the hot solution aqueous barium hydroxide was added until the pH was 5. The solution was then filtered, and barium was removed from the soluble barium salts of organic acids by addition of a slight excess of N-sulphuric acid. Barium sulphate was removed on the centrifuge, and the clear solution was extracted continuously with ether in order to eliminate any glyceraldehyde and acids formed after hydrolysis of the oxidised polysaccharide. As only a small amount of organic acid was extracted, this operation was omitted in subsequent experiments. The glucose determination was carried out by the new paper chromatogram method (Partridge, *loc. cit.*; Flood, Hirst, and Jones, *loc. cit.*). The following quantities of glucose were found (calculated on 100 g. of starch): potato starch, 1·1 g.; acorn starch, 1·8 g.; sago starch, 1·2 g.

One of us (A. J. R.) wishes to thank M. l'Inspecteur Général J. Desmaroux, Directeur du Laboratoire Central des Services Chimiques de l'État in Paris, and the Service des Missions à l'Étranger of the French Ministère des Finances for facilitating his visit to England.

THE UNIVERSITY, MANCHESTER. [*Received, December 8th*, 1947.]

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360. *Studies in the Sterol Group. Part XLVII. A New Route to 7-Dehydrocholesterol (Provitamin D_3) and its Derivatives.**

By A. E. BIDE, H. B. HENBEST, E. R. H. JONES, R. W. PEEVERS, and P. A. WILKINSON.

The methods hitherto available for converting sterols into their 7-dehydro-derivatives are reviewed. Bromination of cholesteryl acetate (III) with *N*-bromosuccinimide gives 7-bromocholesteryl acetate (VII; R = OAc) which on treatment with diethylaniline followed by hydrolysis gives a mixture of 7-dehydrocholesterol (VIII; R = OH) and cholesta-4 : 6-dien-3(β)-ol (IX; R = OH). The overall yield of the dehydro-sterol, based on cholesterol, is about 30%. Cholesteryl benzoate, chloride, and bromide similarly yield 7-bromo-derivatives which are converted into 7-dehydro-compounds on dehydrobromination.

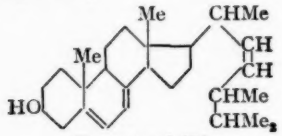
As a result of animal nutrition experiments (*inter al.*, Waddel, *J. Biol. Chem.*, 1934, **105**, 711), particularly with rats and chickens kept on a vitamin-D-deficient diet, it gradually became apparent that the vitamin D of fish-liver oils was not identical with the vitamin D_2 (calciferol) (II), obtained by irradiating ergosterol (I). In 1935, Windaus, Lettré, and Schenck (*Annalen*, **520**, 98) described the preparation from cholesteryl acetate (III), by the route indicated below, of the so-called 7-dehydrocholesterol (IV) which on irradiation gave a highly antirachitic product (vitamin D_3) (V) (Windaus, Schenck, and von Werder, *Z. physiol. Chem.*, 1936, **241**, 100). Shortly afterwards Brockmann (*Z. physiol. Chem.*, 1936, **241**, 104; 1937, **245**, 96) isolated vitamin D from tunny- and halibut-liver oils and found that this substance was identical with the vitamin D_3 (V) derived by irradiating Windaus's 7-dehydrocholesterol (IV).

The classical method developed by the Göttingen workers for the preparation of 7-dehydrocholesterol, only however in about 4% yield based on cholesterol, has since been used for the synthesis of several related 7-dehydro-steroids (*inter al.*, Linsert, *Z. physiol. Chem.*, 1936, **241**, 125; Wunderlich, *ibid.*, p. 116; Haslewood, *Biochem. J.*, 1939, **33**, 454; Butenandt, Hausmann, and Paland, *Ber.*, 1938, **71**, 1316; Ruigh, *J. Amer. Chem. Soc.*, 1942, **64**, 1900; Bergmann, Lyon, and McLean, *J. Org. Chem.*, 1944, **9**, 290), but the yields have not been appreciably improved, although a number of valuable and interesting minor modifications have been made. Thus Haslewood (*J.*, 1938, 224) observed that treatment of a dibenzoate such as that of (IIIa) with boiling dimethylaniline gave an improved yield of the monobenzoate of the dehydro-steroid, and Wintersteiner and Ruigh (*J. Amer. Chem. Soc.*, 1942, **64**, 1177) used the same procedure

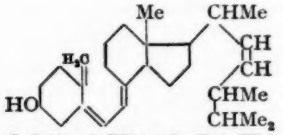
* Cf. *Nature*, 1946, **158**, 169; B.P. 574,432 and other patents pending.

with the 7-monobenzoate; this latter method is probably the best hitherto available of converting Δ^5-steroids into their $\Delta^{5:7}$-dehydro-derivatives.

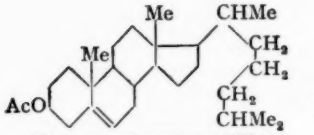
A number of direct dehydrogenation methods of preparing 7-dehydrocholesterol have been described but the yields do not appear to be very satisfactory. Thus Milas and Heggie (*J. Amer. Chem. Soc.*, 1938, **60**, 984; cf. Sah, *Rec. Trav. chim.*, 1940, **59**, 454; Mazza and Migliardi, *Chem. Abs.*, 1943, **37**, 3762) treated cholesteryl acetate with a variety of reagents including benzoquinone and chloranil, and obtained up to 8% conversions into the dehydro-acetate, estimated spectrographically.



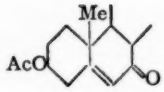
Ergosterol (I.)

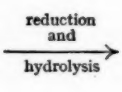


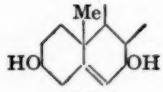
Calciferol (Vitamin D_2) (II.)



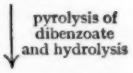
Cholesteryl acetate (III.)

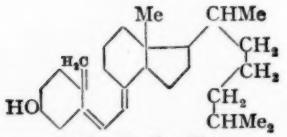




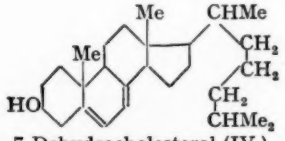


(III*a*.)





Vitamin D_3 (V.)



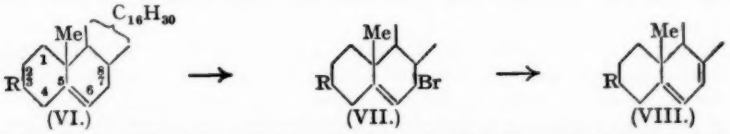
7-Dehydrocholesterol (IV.)

It seemed possible that by employing *N*-bromosuccinimide (Ziegler, *Annalen*, 1942, **551**, 80) 4- and/or 7-bromo-compounds could be obtained from cholesteryl esters and that on subsequent removal of hydrogen bromide the 7-bromo-compounds would yield 7-dehydrocholesteryl esters. Cholesteryl acetate (VI; R = OAc) was found to react at widely varying rates with *N*-bromosuccinimide suspended in various media. By working under carefully controlled conditions with light petroleum, it was eventually possible to isolate a crystalline monobromo-compound (m. p. 109°; $[\alpha]_D^{20°}$ — 245°) in 30—42% yield. A further considerable quantity of this bromo-compound remained in the mother liquors (as shown by the reaction with piperidine, forthcoming publication), but it could not be separated from the other substances present. Although there is little doubt that polybromination of cholesteryl acetate does occur when excess of *N*-bromosuccinimide is employed, attempts further to brominate the monobromo-compound with this reagent were unsuccessful, and no pure dibromo-compound could be isolated.

Of the various possible structures for this bromo-compound the epimeric 4-bromo- and 7-bromo-cholesteryl acetates were the first to be considered, although structures such as 5-bromo-Δ^6- and 6-bromo-Δ^4-cholestenyl acetates, arising from anionotropic rearrangements of primary bromination products, were not overlooked. On the basis of a considerable amount of evidence, presented in this and the three following papers, the crystalline bromo-compound is formulated as " β "-7-*bromocholesteryl acetate* (VII; R = OAc).* The main arguments may be summarised as follows. Dehydrobromination followed by hydrolysis (see below) gives 7-dehydrocholesterol, 7-substituted cholesterol derivatives are obtained in substitution reactions (see Part XLIX, this vol., p. 1792), and conversely, halogenation of 7-hydroxycholesterol derivatives gives halogeno-compounds of the same series (see Part XLVIII, following paper). This

* It is now generally accepted practice in the steroid series to denote stereochemical configuration in relation to the angular methyl group at C_{10} by the suffixes (α) and (β). Thus " 3(β)-hydroxy " implies that the 3-hydroxyl group is on the same side of the plane of the steroid molecule as the C_{10} methyl group, and further it is arbitrarily assumed that, with the steroid formula written in the conventional manner, the hydroxyl and methyl groups project *above* the plane of the paper (represented by a full-line bond). For a full account of these conventions see Shoppee, *Ann. Reports*, 1946, **43**, 200. For 7-substituted sterol derivatives (as distinct from the bile-acid series), configuration relative to the C_{10} methyl group has yet to be established with certainty and hence the use of the conventional method of

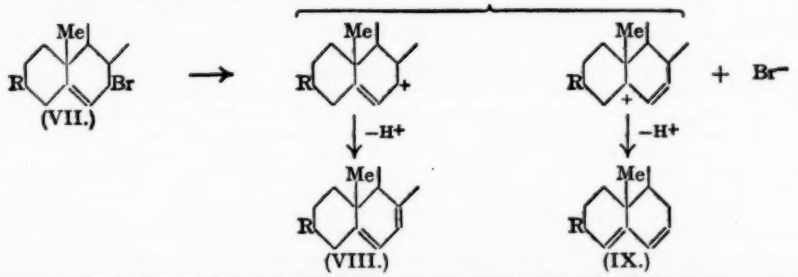
bromination reaction is superficially analogous to the chromic acid oxidation of cholesteryl acetate which leads to the 7-keto-derivative (Windaus, Lettré, and Schenck, *loc. cit.*) in contrast to oxidation with selenium dioxide which involves substitution in the 4-position (Rosenheim and Starling, *J.*, 1937, 377; Petrow, Rosenheim, and Starling, *J.*, 1938, 677; Paige, *J.*, 1943, 437).



Cholesteryl benzoate (VI; R = OBz), cholesteryl chloride, and cholesteryl bromide have also been brominated in the same manner, but with these the reactions proceeded too slowly in the lower-boiling solvents, and light petroleum (b. p. 80—100°) or carbon tetrachloride was employed. By analogy with the cholesteryl acetate product, and on dehydrobromination and other evidence, the crystalline bromo-compounds obtained are formulated as "β"-*7-bromocholesteryl benzoate* (VII; R=OBz), "β"-*7-bromocholesteryl chloride* (VII; R=Cl), and "β"-*7-bromocholestery bromide* (VII; R = Br) respectively. The yields of these products were somewhat higher than those obtained when working with the acetate, and this is attributed to their rather greater stability and crystallising tendencies, resulting in easier isolation from the crude reaction products.

Extensive studies have been made of the dehydrobromination of the bromo-acetate (VII; R = OAc), followed by hydrolysis, to 7-dehydrocholesterol (provitamin D_3) (VIII; R = OH). The proportion of the latter compound in reaction products can readily be ascertained spectrographically, since it exhibits a characteristic triplet band with maxima at 2700, 2810, and 2920 A. The bromo-compound reacts with primary and secondary amines to give amino-steroids (forthcoming publication), but with tertiary amines at moderate temperatures the bromo-steroid undergoes a smooth dehydrobromination reaction. The proportion of 7-dehydrocholesterol in the final product varies considerably, however, with the nature of the tertiary amine employed. Diethylaniline was found to give a 40—50% yield of dehydrosterol, estimated spectrographically, and this was confirmed by isolation of the 7-dehydrocholesterol as its sparingly soluble 3 : 5-dinitrobenzoate (Windaus, Lettré, and Schenck, *loc. cit.*) which was subsequently hydrolysed by the method of Huber, Ewing, and Kriger (*J. Amer. Chem. Soc.*, 1945, **67**, 609).

The nature of the remainder of the dehydrobromination product was of interest. It was observed that in the crude hydrolysed product the characteristic light-absorption band of the 7-dehydrocholesterol was invariably accompanied by a high-intensity maximum at 2400 A. The material responsible for this absorption could not readily be isolated from the product obtained by treatment with diethylaniline, but other bases gave products with rather more intense maxima in the 2400 A. region, and, from an experiment using 2 : 6-lutidine, cholesta-4 : 6-dien-3(β)-ol (IX; R = OH) was isolated in about 65% yield. This substance had been described previously by Petrow (*J.*, 1940, 66) and Spring and Swain (*J.*, 1941, 320), and these authors noted its high-intensity absorption at 2390 A. The simultaneous formation of these two dehydrosterols by dehydrobromination of the 7-bromo-compound is clearly in accordance with the ionisation (E_1) mechanism of elimination reactions (Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 657; Hughes, *J.*, 1946, 968), *viz.* :



representing stereochemical configuration (*e.g.*, 7(β)-bromo-, etc.) is unjustifiable. For this reason it has been decided to use the above notation, *e.g.*, "β"-7-bromo- (cf. Petrow and Starling, *J.*, 1946, 749), which is not intended to have any absolute significance, but does serve to relate 7-substituted sterols to the epimeric and trivially named α- and β-7-hydroxycholesterols described some years ago (Windaus, Lettré, and Schenck, *loc. cit.*; Barr, Heilbron, Parry, and Spring, *J.*, 1936, 1437) before the present system became generally adopted. The stereochemistry of the 7-substituted sterols is discussed more fully in Parts XLVIII and XLIX (following papers).

The preponderance of the $\Delta^{4:6}$-isomer (IX; R = OH) under most conditions is doubtless related to the relatively greater stability of systems containing conjugated double bonds distributed between two rings. Although a large number of tertiary bases have been examined as dehydrobrominating agents no correlation between the relative proportions of the alcohols (VIII) and (IX) and base strengths has been discerned, and it seems certain that other factors, especially of a steric nature, are involved.

Dehydrobromination of the bromo-benzoate (VII; R = OBz) with diethylaniline gave a product containing the benzoates (VIII and IX; R = OBz) in the ratio of about 1 : 4, and when using 2 : 6-lutidine it was possible to isolate some of the cholesta-4 : 6-dienyl benzoate (IX; R = OBz) by crystallisation. Treatment of 7-bromocholesteryl chloride and the corresponding bromide with diethylaniline yielded *7-dehydrocholesteryl chloride* (VIII; R = Cl) and *7-dehydrocholesteryl bromide* (VIII; R = Br), with light-absorption properties very similar to those of 7-dehydrocholesterol. These materials could be separated from some contaminant (probably a cholestatriene) only with considerable loss.

After the researches described in this and the following three papers had been finished and the writing of the papers almost completed, our attention was directed to a publication by Buisman, Stevens, and Vliet (*Rec. Trav. chim.*, **1947**, **66**, 83) entitled " A New Synthesis of 7-Dehydrocholesterol ". These authors decided to publish these " preliminary results " in view of the appearance of our earlier note (*Nature, loc. cit.*). In principle the synthesis is identical with the new route described in our preliminary account and in more detail above. However, since our study appears to have been more comprehensive and brought to a greater degree of completion it was decided not to alter our papers in any way but to discuss the common features here and also at the end of Part XLIX (*loc. cit.*).

The bromination procedure of Buisman *et al.* involves the use of carbon tetrachloride, as originally recommended by Ziegler, and the Dutch workers have found it advantageous to employ ultra-violet irradiation to accelerate the reaction (cf. Meystre *et al.*, *Helv. Chim. Acta*, **1945**, **28**, 1252). It seems probable that the somewhat impure nature of the bromination product from cholesteryl benzoate and their failure to obtain a crystalline product by the bromination of cholesteryl acetate may be attributable to these variations in experimental conditions.

The Dutch workers have also found tertiary amines to be most suitable as dehydrobrominating agents, but in our experience *s*-collidine does not yield such satisfactory results as diethylaniline. They appreciated the presence of another sterol (absorbing below 2500 A.) accompanying 7-dehydrocholesterol in the dehydrobromination product, and suggested that it might be cholesta-4 : 6-dien-3(β)-ol; in this paper this has been proved conclusively.

Experimental.

In this and the following three papers, rotations were measured in chloroform solutions (l = 1 dcm.), and light-absorption data were determined on alcoholic solutions except where otherwise mentioned.

" *β* "-*7-Bromocholesteryl Acetate* (VII; R = OAc).—Finely powdered *N*-bromosuccinimide (28 g.; 1·2 mols.) was added to a solution of cholesteryl acetate (56 g.) in light petroleum (250 c.c.; b. p. 60—80°), and the mixture was refluxed on the steam-bath with vigorous mechanical stirring. The reaction began slightly exothermically with the development of a yellow colour which deepened during the reaction, and, with some batches of material, the succinimide formed as a voluminous crystalline deposit. The correct reaction time was ascertained by filtering the cooled reaction mixture, washing the succinimide with light petroleum (b. p. 60—80°), and weighing the dried material. When the time of reaction was such that the weight of succinimide corresponded to complete bromine uptake, this reaction time was used in subsequent preparations using these particular batches of materials.

The filtered petroleum solution was evaporated under reduced pressure (water-pump) to remove most of the solvent. The residue was dissolved in acetone (25 c.c.) and again evaporated under reduced pressure to remove the residual petroleum. The orange-brown gum ($[\alpha]_D^{20°}$ *ca.* − 110°) was dissolved in acetone (50 c.c.), and the solution was cooled to 0°, seeded, and left overnight at 0°. The resulting semi-solid mass was then crushed to a slurry of fine crystals and shaken periodically during 6 hours. After cooling to −20°, the bromo-compound was filtered off rapidly through a pre-cooled funnel, washed with cold (− 20°) acetone, thoroughly pressed on the filter, and then dried in a vacuum desiccator. At this stage the product was colourless, and the yield varied from 25 to 35 g. with $[\alpha]_D^{20°}$ − 220° to − 235°. This material was recrystallised by dissolving it in about 250 c.c. of light petroleum (b. p. 40—60°) by slight warming, cooling to 0° to start crystallisation, and finally cooling to − 40°. The bromo-compound was filtered off rapidly and washed with the minimum quantity of cold (— 40°) light petroleum (b. p. 40—60°). The " *β* "-*7-bromocholesteryl acetate* (20—28 g., *i.e.*, 30—42%) so obtained formed a microcrystalline powder, m. p. 109—110°; $[\alpha]_D^{20°}$ − 245° (*c*, 1·28). Slow crystallisation from dilute solutions in the same solvent gave the bromo-compound in poor yield as long needles, with the same physical constants (Found : C, 68·3; H, 9·4; Br, 15·3, 16·0. $C_{29}H_{47}O_2Br$ requires C, 68·6; H, 9·3; Br, 15·7%). The bromo-compound decomposes slowly at room temperature, an odour of acetic acid soon becoming apparent. It is stable for many weeks at 0°.

"β"-7-*Bromocholesteryl Benzoate* (VII; R = OBz).—A mixture of cholesteryl benzoate (15 g.), finely powdered *N*-bromosuccinimide (7·5 g.; 1·38 mols), and light petroleum (b. p. 80—100°) (150 c.c.) was heated to boiling with vigorous stirring; reaction soon started with the development of a yellow colour. The mixture was refluxed with stirring for 5 minutes, cooled to 40°, and filtered, the succinimide being washed with light petroleum, dried, and weighed (4·0 g.). The solvent was removed under reduced pressure, the orange gum so obtained was dissolved in acetone (100 c.c.), and after crystallisation had been initiated the mixture was kept at room temperature for 1 hour with intermittent shaking. Recrystallisation of the resulting solid from acetone–ethyl acetate (1 : 1) gave slightly impure bromobenzoate (5·8 g.), m. p. 136—140°. This material was dissolved in warm benzene (7·5 c.c.); addition of acetone (20 c.c.) and cooling to 0° gave "β"-7-*bromocholesteryl benzoate* (3·7 g.), m. p. 140°; $[\alpha]_D^{18°}$ − 172° (*c*, 1·01) (Found: C, 72·0; H, 8·5. $C_{34}H_{49}O_2Br$ requires C, 71·7; H, 8·7%).

"β"-7-*Bromocholesteryl Chloride* (VII; R = Cl).—A solution of cholesteryl chloride (50 g.) in petroleum (200 c.c.; b. p. 80—100°) was refluxed with finely powdered *N*-bromosuccinimide (25 g.; 1·14 mols.) with vigorous stirring for 20 minutes; it was then cooled and filtered, giving succinimide (13·3 g.; 95%). The filtrate was evaporated under reduced pressure, and the residue dissolved in acetone (200 c.c.). The bromo-compound (32·3 g., m. p. 139°) soon started to crystallise; it was recrystallised by dissolving it in warm benzene (50 c.c.) and adding acetone (50 c.c.); "β"-7-*bromocholesteryl chloride* (26·7 g.) was obtained as granular prisms, m. p. 142°; $[\alpha]_D^{20°}$ − 242° (*c*, 1·09) (Found: C, 67·0; H, 9·05. $C_{27}H_{44}ClBr$ requires C, 67·0; H, 9·2%).

Improved Preparation of Cholesteryl Bromide.—A solution of cholesterol (50 g.) in chloroform (100 c.c.) and diethylaniline (20 c.c.) was rapidly stirred and cooled (ice) while a solution of thionyl bromide (12 c.c.; 1·2 mols.) in chloroform (38 c.c.) was added during 20 minutes, the internal temperature being kept at 15—20°. After being stirred for an hour at 20° the solution was poured slowly with stirring into alcohol (500 c.c.), and the precipitation was completed by keeping at 0° overnight. The solid (41 g.; m. p. 94—96°, softens at *ca.* 84°) was filtered off and recrystallised from acetone (300 c.c.), giving fairly pure cholesteryl bromide (34 g.) as plates, m. p. 97—99°. (If this crystallisation mixture is allowed to stand too long or cooled below room temperature there is a tendency for an impurity to crystallise out as needles, m. p. 82—84°, after the plates of cholesteryl bromide have separated.) Further crystallisation of the product yielded pure cholesteryl bromide (26·5 g.), m. p. 100—102°, $[\alpha]_D^{20°}$ − 21·6° (Kolm, *Monatsh.*, 1912, **33**, 447, gives m. p. 98°, $[\alpha]_D^{19°}$ − 19·1°; Marker *et al.*, *J. Amer. Chem. Soc.*, 1936, **58**, 338, give m. p. 96°; Heilbron *et al.*, *J.*, 1936, 907, give $[\alpha]_D$ − 20·8°).

"β"-7-*Bromocholesteryl Bromide* (VII; R = Br).—A solution of cholesteryl bromide (40 g.) in redistilled carbon tetrachloride (180 c.c.) was refluxed with finely powdered *N*-bromosuccinimide (16 g.; 1·0 mol.) with vigorous stirring for 25 minutes. On cooling and filtering, 9·02 g. of succinimide were obtained, and the filtrate was evaporated under reduced pressure. The residue was dissolved in acetone (125 c.c.) and cooled to 0° overnight. The crystalline product (34·3 g.; m. p. 140—142°), after several recrystallisations from light petroleum (b. p. 60—80°), gave "β"-7-*bromocholesteryl bromide* (14 g.) as needles, m. p. 145° (decomp.); $[\alpha]_D^{20°}$ − 205° (Found: C, 61·5; H, 8·35; Br, 30·55. $C_{27}H_{44}Br_2$ requires C, 61·35; H, 8·4; Br, 30·25%).

Dehydrobromination of "β"-7-Bromocholesteryl Acetate.—(a) *With diethylaniline.* (i) A mixture of "β"-7-bromocholesteryl acetate (6 g.) and diethylaniline (10 c.c., once distilled from sodium) was heated on the steam-bath for 3 hours; diethylaniline hydrobromide began to crystallise out after 10 minutes. The cooled mixture was treated with light petroleum (100 c.c.; b. p. 40—60°), allowed to stand for 30 minutes, and then filtered, giving 2·45 g. of diethylaniline hydrobromide (theoretical, 2·72 g.). The petroleum solution was washed with hydrochloric acid (10%) until the excess of diethylaniline had been removed; during this washing some white amorphous material separated. After being washed with sodium hydrogen carbonate solution, the petroleum solution was filtered and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a gum (5 g.) that readily solidified. Absorption-spectrum assay indicated the presence of approximately 40% of 7-dehydrocholesteryl acetate and about 45% of cholesta-4 : 6-dienyl acetate.

The dehydrobrominated product (5 g.) was hydrolysed by refluxing it with potassium hydroxide (1 g.) in methanol for 30 minutes. The steroid (4·6 g., 45% 7-dehydrocholesterol *) was crystallised from methanol to give a crystalline product (2·8 g.), containing *ca.* 55% of 7-dehydrocholesterol.* This (2·6 g.) was treated with 3 : 5-dinitrobenzoyl chloride (2 g.) in dry pyridine (40 c.c.) at room temperature for 3 days. Ice and water were added, and the solid product was filtered off, washed with sodium hydrogen carbonate solution, and then treated with acetone (30 c.c.) at room temperature for 3 hours. The insoluble yellow solid was crystallised from chloroform–acetone to give 7-dehydrocholesteryl 3 : 5-dinitrobenzoate (1·24 g.) as yellow needles, m. p. 206°, undepressed on admixture with an authentic specimen; $[\alpha]_D^{20°}$ − 43° (*c*, 0·76). Light absorption: Maxima, 2820 and 2970 A.; ϵ = 12,500 and 6500 respectively {Windaus, Lettré, and Schenck, *Annalen*, 1935, **520**, 98, give m. p. 207°, $[\alpha]_D^{20°}$ − 45·7° (*c*, 1·64)}.

(ii) "β"-7-Bromocholesteryl acetate (3 g.) was dehydrobrominated with diethylaniline (5 c.c.) as described above. The crude sterol (2·5 g.) obtained by alkaline hydrolysis, and containing approximately 40% of dehydrocholesterol,* was allowed to stand at room temperature for 48 hours with 3 : 5-dinitrobenzoyl chloride (3 g.) and pyridine (15 c.c.). The ester obtained by dilution with ice and water was washed successively with sodium hydrogen carbonate solution, methanol, and acetone until the washings were colourless. The product was dissolved in hot chloroform (20 c.c.) and filtered; acetone (5 c.c.) was added, and the solution cooled (finally to 0°) to give the crystalline 3 : 5-dinitrobenzoate (1·21 g.) with the same physical constants as the material from the above preparation. The overall yield of 7-dehydrocholesterol isolated as the 3 : 5-dinitrobenzoate was 35%, agreeing well with the estimated content of 40% in the crude material.

(b) *With 2 : 6-lutidine.* A mixture of "β"-7-bromocholesteryl acetate (3 g.) and 2 : 6-lutidine (5 c.c.) was heated at 100° for 1 hour, the hydrobromide starting to separate after a few minutes. The mixture was diluted with light petroleum (b. p. 40—60°), and the steroid acetate, which would not

* 7-Dehydrocholesterol content computed from light-absorption data.

crystallise, isolated in the usual way. It was refluxed with a solution of potassium hydroxide (0·3 g.) in methanol (50 c.c.) for 30 minutes. Water (5 c.c.) was added, and the solution cooled to 0° to give a sterol mixture (1·8 g.), m. p. 85—90°, which was recrystallised from methanol to give cholesta-4 : 6-dien-3(β)-ol (1·5 g.), m. p. 120°, unchanged on further crystallisation (Petrow, *J.*, 1940, 66, gives m. p. 126—127°; Spring and Swain, *J.*, 1941, 320, give m. p. 119—120°).

The cholesta-4 : 6-dienol (m. p. 120°; 0·6 g.) was dissolved in a mixture of acetic anhydride (2·5 c.c.) and dry pyridine (5 c.c.) and kept overnight at room temperature. The product, isolated with ether, solidified on standing at 0°, and two recrystallisations from methanol–acetone (1 : 1) gave cholesta-4 : 6-dienyl acetate (0·25 g.), m. p. 77°, $[\alpha]_D^{20°}$ − 63° (*c*, 0·54). Light absorption: Maximum, 2400 A.; ϵ = 26,000 (Petrow, *loc. cit.*, gives m. p. 78—79°, $[\alpha]_D^{20°}$ − 71·6°. Light absorption: Maximum, 2390 A.; ϵ = 26,000. Spring and Swain, *loc. cit.*, give m. p. 77—78°, $[\alpha]_D$ − 67°. Light absorption: Maximum, 2390 A.; ϵ = 22,000).

Dehydrobromination of "β"-7-Bromocholesteryl Benzoate.—(a) *With diethylaniline.* The benzoate (1 g.) and redistilled diethylaniline (2·5 c.c.) were heated on the steam-bath for 4 hours. Dilution with 50 c.c. of light petroleum (b. p. 40—60°) precipitated diethylaniline hydrobromide (0·36 g., 89% theoretical). After the excess of diethylaniline had been removed by washing with dilute hydrochloric acid, the solvent was removed under reduced pressure, leaving a residue which readily solidified. This product had light absorption corresponding to about 30% of 7-dehydrocholesteryl benzoate. Recrystallisation from acetone did not alter the composition of the above mixture appreciably.

(b) *With 2 : 6-lutidine.* A mixture of the benzoate (0·5 g.) and 2 : 6-lutidine (2 c.c.) was heated on the steam-bath for 2 hours, after which the steroid was isolated with ether. (Some material insoluble in both the ether and the aqueous layer was removed by filtration.) Two recrystallisations from acetone–methanol (2 : 1) gave a poor yield of cholesta-4 : 6-dienyl benzoate (72 mg.) as plates, m. p. 126°; $[\alpha]_D^{16°}$ − 92° (*c*, 2·05). Light absorption: Maximum, 2370 A.; ϵ = 34,500.

7-Dehydrocholesteryl Chloride (VIII; R = Cl).—A mixture of powdered "β"-7-bromocholesteryl chloride (12 g.) and diethylaniline (25 c.c.) was heated on the steam-bath for 6 hours. Cooling, followed by the addition of light petroleum (100 c.c.; b. p. 40—60°), gave 5·3 g. of diethylaniline salts. Isolation of the steroid in the usual way gave a product which had light absorption corresponding to about 40% 7-dehydrocholesteryl chloride. Trituration of the product with cold acetone gave a powdery solid, containing very little cholestatriene, which after three crystallisations from acetone gave *7-dehydrocholesteryl chloride* (1·15 g.) in long needles, m. p. 132°; $[\alpha]_D^{16°}$ − 100° (*c*, 1·12) (Found: C, 80·4; H, 10·7. $C_{27}H_{43}Cl$ requires C, 80·45; H, 10·75%). Light absorption in chloroform: Maxima, 2770, 2840 and 2960 A.; ϵ = 11,000, 12,000 and 7,500 respectively.

7-Dehydrocholesteryl Bromide (VIII; R = Br).—A solution of "β"-7-bromocholesteryl bromide (34 g.) in diethylaniline (75 c.c.) was heated at 95° for 3 hours. Cooling, followed by the addition of light petroleum (250 c.c.; b. p. 60—80°), gave diethylaniline hydrobromide (15·5 g.). Isolation of the steroid in the usual way gave, after crystallisation from acetone, a product (10·4 g.), m. p. 136—140°, which had light absorption in *cyclo*hexane corresponding to a 7-dehydrocholesteryl bromide content of about 80%. However, it was not readily separated from an impurity by crystallisation, and two recrystallisations from ethyl acetate (100 c.c.) were required in order to obtain pure *7-dehydrocholesteryl bromide* (2·9 g.) as needles, m. p. 147—148°, $[\alpha]_D^{20°}$ − 86° (*c*, 4·2) (Found: C, 72·75; H, 9·6; Br, 17·65. $C_{27}H_{43}Br$ requires C, 72·45; H, 9·7; Br, 17·85%). Light absorption in *cyclo*hexane: Maxima, 2750, 2850, and 2970 A.; ϵ = 13,000, 13,500 and 9,000 respectively.

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361. *Studies in the Sterol Group. Part XLVIII. 7-Substituted Cholesterol Derivatives and their Stereochemistry (Part I). 7-Halogeno-derivatives.*

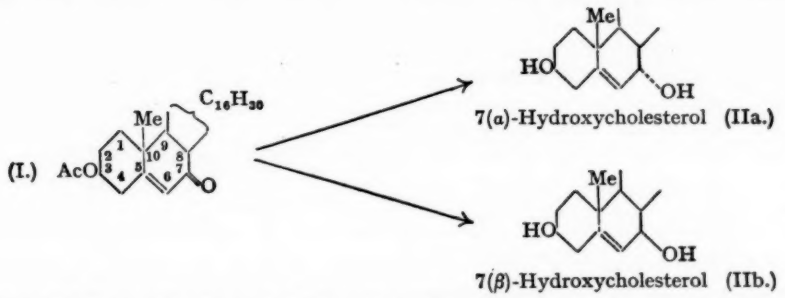
By A. E. Bide, H. B. Henbest, E. R. H. Jones, and P. A. Wilkinson.

The stereochemistry of 7-substituted cholesterol derivatives is reviewed. Attention is drawn to the unusually large optical rotation differences observed between epimerides in the 7-position and it is suggested that the sign of rotation provides a definite indication of their relative stereochemical configuration. The absolute configuration of these 7-substituted cholesterol derivatives is discussed.

In the preceding paper the preparation of "β"-7-bromocholesteryl esters by bromination of cholesteryl esters with *N*-bromosuccinimide has been described and for comparison purposes a number of 7-halogeno-compounds have now been made from the corresponding 7-hydroxy-compounds by employing thionyl chloride or phosphorus halides. It appears that the 7-halogeno-compounds with the "β"-configuration are inherently more stable than the "α"-epimerides.

Much of the work carried out hitherto on 7-substituted cholesterol derivatives has involved the use, as starting material, of the readily accessible 7-ketocholesteryl acetate (I), first obtained by

Mauthner and Suida (*Monatsh.*, 1896, **17**, 593) by oxidation of cholesteryl acetate with chromic acid, this preparation being subsequently improved by Windaus, Lettré, and Schenck (*Annalen*, 1935, **520**, 98). The latter authors reduced this keto-acetate with aluminium *iso*propoxide and *iso*propyl alcohol and obtained, after hydrolysis, one of the two possible 7-hydroxycholesterols (IIa or IIb), m. p. 178°. The second isomer, m. p. 186°, was subsequently obtained in small



yield by Barr, Heilbron, Parry, and Spring (*J.*, 1936, 1437) by oxidising cholesteryl hydrogen phthalate with potassium permanganate, followed by hydrolysis. A more recent and more detailed study of the Meerwein–Ponndorf reduction of the keto-acetate (I) by Wintersteiner and Ruigh (*J. Amer. Chem. Soc.*, 1942, **64**, 1177, 2453) has revealed, as would be expected, that the epimeric 7-hydroxy-compounds are in fact produced simultaneously, the second form (m. p. 186°), however, only in minor proportion. Ruzicka, Prelog, and Tagmann (*Helv. Chim. Acta*, 1944, **27**, 1149) have shown that an equilibrium is set up when either of these diols is refluxed in acetic acid solution, the equilibrium mixture containing about 65% of the Windaus diol.

The convention now generally adopted for representing the stereochemical configuration of substituted steroids, namely, by suffixing with (α) or (β) the number of the nuclear carbon atom carrying the substituent, has been briefly described in the preceding paper. An excellent detailed account has been given recently by Shoppee (*Ann. Reports*, 1946, **43**, 200). Windaus *et al.* (*loc. cit.*) had no knowledge of the configuration of their diol (m. p. 178°) relative to the C_{10} methyl group, but rather unfortunately they designated it 7(α)-hydroxycholesterol. On the other hand, Heilbron *et al.* (*loc. cit.*), recognising that the true configuration of the 7-hydroxyl group in their diol was unknown, termed the latter β-7-hydroxycholesterol. In the present series of papers the nomenclature " α "-7- and " β "-7-hydroxycholesterols is used for the above diols and for their derivatives; in this way not only is the absence of information concerning orientation relative to the C_{10} methyl group made clear, but relationships to the original epimeric diols can thus be indicated.

Comparison of the optical rotations of the epimeric 7-hydroxycholesterols and their simple esters (Table I) reveals that the " α "-diol and its derivatives are uniformly dextrorotatory whereas the compounds of the " β "-group are lævorotatory :

TABLE I.

" α "-Series.	$[\alpha]_D$ in $CHCl_3$.	" β "-Series.	$[\alpha]_D$ in $CHCl_3$.
" α "-7-Hydroxycholesterol	+ 7·2° [1]	" β "-7-Hydroxycholesterol	− 86·4° [4]
	+ 4° [2]		− 87·6° [1]
,, diacetate	+51·8° [1]	,, diacetate	−174·6° [4]
,, dibenzoate	+94·3° [3]		−177° [2]
	+94° [2]	,, dibenzoate	−107·5° [1]

[1] Wintersteiner and Ruigh, *loc. cit.*, p. 2453.
[2] Ruzicka, Prelog, and Tagmann, *loc. cit.*
[3] Windaus, Lettré, and Schenck, *loc. cit.*
[4] Barr, Heilbron, Parry, and Spring, *loc. cit.*

The large differences between these epimeric forms [even larger differences are observed with the epimeric 7-amino-compounds and also with their *N*-acetyl derivatives (Barnett, Ryman, and Smith, *J.*, 1946, 524; Eckhardt, *Ber.*, 1938, **71**, 469)] are unusual in the steroid series, but they have been amply confirmed and extended by the values for a number of pairs of new 7-substituted cholesterol derivatives prepared during the present study and described in this and the following papers. The sign of optical rotation can only rarely be employed as an indication of configuration, but the differences here are so marked that it can safely be

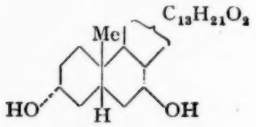
postulated as a general rule that " α "-7-substituted cholesterol derivatives are dextrorotatory while the " β "-7-compounds are lævorotatory. [A list of the 7-derivatives now known, together with their optical rotations, is given in the Table in Part L, this vol., p. 1798.]

The marked differences in optical rotatory properties between epimeric 7-substituted cholesterol derivatives must be connected with some " vicinal action " (cf. Barton and Jones, *J.*, 1944, 659; Barton, *J.*, 1945, 813; 1946, 512; Barton and Cox, *Nature*, 1947, **159**, 470) of the 5 : 6-double bond, since much smaller differences (see Table II) are observed between the epimeric dihydro-compounds [prepared by Wintersteiner and Moore (*J. Amer. Chem. Soc.*, 1943, **65**, 1503) by the catalytic hydrogenation of 7-ketocholestanol], although even these are large

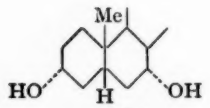
TABLE II.

	Cholestane $[\alpha]_D$ in $CHCl_3$.	Cholest-5-ene $[\alpha]_D$ in $CHCl_3$.
" α "-7-3(β)-Diol	+53°	+ 7°
,, diacetate	+55°	+ 52°
" β "-7-3(β)-Diol	+ 8°	− 87°
,, diacetate	−17°	−175°

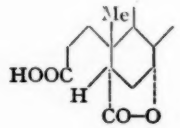
when compared with the values for epimers in the 3-position (Callow and Young, *Proc. Roy. Soc.*, 1936, **157**, *A*, 194). The " vicinal action " may take the form of deflection of valency angles in one or both of the 7-epimers as a result of steric factors. It seems highly probable that the two series of 7-hydroxycholestanol derivatives are related to their 7-hydroxycholesterol analogues in the way that the signs of their optical rotation suggest (Wintersteiner and Moore, *loc. cit.*), but confirmation of this by hydrogenation of the cholest-5-ene compounds is unfortunately impossible since hydrogenation results in removal of the 7-substituent in all the instances so far studied (Barr, Heilbron, Parry, and Spring, *loc. cit.*; Wintersteiner and Ruigh, *loc. cit.*; see also Part L, *loc. cit.*).



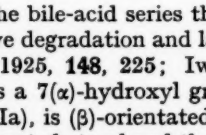
(IIIa.)



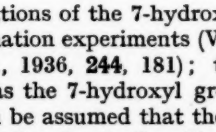
(IIIb.)



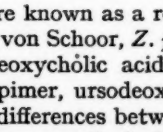
In the bile-acid series the configurations of the 7-hydroxyl groups are known as a result of oxidative degradation and lactone formation experiments (Windaus and von Schoor, *Z. physiol. Chem.*, 1925, **148**, 225; Iwasaki, *ibid.*, 1936, **244**, 181); thus chenodeoxycholic acid (IIIb) contains a 7(α)-hydroxyl group whereas the 7-hydroxyl group in its epimer, ursodeoxycholic acid (IIIa), is (β)-orientated. If it can be assumed that the structural differences between the hydrogenated sterol and the bile acid series, *i.e.*, in the side chains and more particularly at C_5, do not exert any appreciable effect on molecular rotation differences between epimeric pairs of 7-substituted compounds, then the conclusions of Plattner and Heusser (*Helv. Chim. Acta*, 1944, **27**, 748), based on these differences [+ 175° (in alcohol) between cheno- and urso-deoxycholic acids and − 181° (in chloroform) between the " α "-7- and " β "-7-hydroxycholestanols], lead to the determination of configuration in these hydroxycholestanols. The arbitrary assignments " α "-7- and " β "-7- used in these papers, and in various forms by other workers, would thus need to be reversed in order to designate the configuration relative to the C_{10} methyl group. However, as has been pointed out by Shoppee (*Ann. Reports, loc. cit.*), the further extension of these assumptions to the 7-hydroxycholesterols is at variance with conclusions based upon the relative ease of elimination of benzoic acid from isomeric 7-benzoyloxycholesterol derivatives (Wintersteiner and Ruigh, *loc. cit.*), and, although it is conceivable that the usually facile *trans*-elimination may be swamped by steric factors, some more rigid proof of the configurations of the 7-substituted sterol derivatives is highly desirable.



(IV.)



(V.)

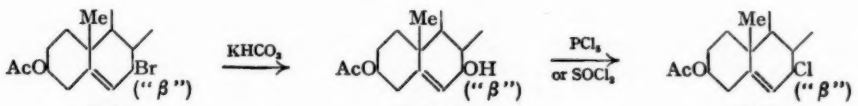


(VI.)

In the preceding paper preparations of monobromo-compounds by the action of *N*-bromosuccinimide on cholesteryl acetate, benzoate, chloride, and bromide are described, and these

compounds have all been formulated as belonging to the " β "-7- series. In order to accumulate evidence in support of these formulations the preparation of epimeric 7-halogeno-derivatives by alternative routes has been studied. " α "-7-Hydroxycholesteryl benzoate (IV), prepared by Eckhardt (*loc. cit.*) by the partial benzoylation of the Windaus " α "-7-hydroxycholesterol, was clearly the most convenient starting material for this purpose. Wintersteiner and Moore (*loc. cit.*) had reported that the saturated 7-hydroxycholestanyl esters did not readily yield 7-halogeno-derivatives, but fortunately the behaviour of (IV) was found to be in sharp contrast to these observations. Treatment of the dextrorotatory mono-benzoate (IV) with phosphorus tribromide in ethereal suspension yielded " β "-7-bromocholesteryl benzoate (V), identical with the product obtained (preceding paper) by the reaction of cholesteryl benzoate (VI) with *N*-bromosuccinimide. Similarly, with phosphorus pentachloride the strongly lævorotatory " β "-7-*chlorocholesteryl benzoate* was produced. It seems quite clear that stereochemical inversions must be involved in these substitution reactions with the phosphorus halides. Experiments in which phosphorus trichloride or thionyl chloride was employed yielded non-homogeneous products which, according to their specific rotations, appeared to be mixtures of the epimeric " α "- and " β "-7-chloro-compounds. However, by treating a pyridine solution of the monobenzoate (IV) with thionyl chloride at 0° it was possible to isolate the dextrorotatory " α "-epimer, " α "-7-*chlorocholesteryl benzoate*, as the major product of the reaction.

From a study of the mild alkaline hydrolysis of " β "-7-bromocholesteryl acetate (VII), the corresponding lævorotatory " β "-7-hydroxycholesteryl acetate (VIII) became available (described in Part XLIX). Treatment of this monoacetate with either thionyl chloride



(VII.) (VIII.) (IX.)

or phosphorus pentachloride readily gave " β "-7-*chlorocholesteryl acetate* (IX). Thus while phosphorus pentachloride produces substitution with inversion in an " α "-7-hydroxy-compound, and the use of thionyl chloride results in substitution with partial inversion, both reagents effect substitution in the " β "-7-hydroxy-compound without any appreciable inversion of configuration at the 7-position.

These facts, together with the knowledge that bromination with *N*-bromosuccinimide fails to produce any detectable quantities of the " α "-7-bromo-compounds (preceding paper), suggest an inherently greater stability of the 7-halogeno-compounds of the cholesterol series with a " β "-orientation.

The instability of the " β "-7-compounds is apparently only manifest in the transition state in replacement reactions, since treatment of the " α "-7-chloro-benzoate with phosphorus pentachloride fails to effect any isomerisation. It may further be concluded that the difficulty of preparing these " α "-7-compounds, either by replacement from the hydroxy-compounds or by direct bromination with *N*-bromosuccinimide, may result from steric hindrance between the C_{10}(β)-methyl group and the C_7-halogen atom. This would probably be very considerable if the C_7 halogen atoms had the true (β)-configuration, *i.e.*, if they were on the same side of the plane of the steroid molecule as the C_{10}-methyl group. Such a conclusion reinforces the deduction of Plattner and Heusser (*loc. cit.*) that the true C_7 configurations are the reverse of those indicated by the trivial " α " and " β " prefixes.

Treatment of " β "-7-bromocholesteryl acetate (VII) with sodium iodide in acetone gave a quantitative yield of " β "-7-*iodocholesteryl acetate* with the unusually high rotation ($[\alpha]_D^{20°}$) of − 365°. The corresponding *benzoate* was similarly prepared.

The optical rotatory properties of all of the 7-halogeno-cholesteryl esters are collated in the Table in Part L (*loc. cit.*). The identical stereochemical configurations of the " β "-7-chloro-, -bromo-, and -iodo-acetates are strikingly confirmed by their reactions with methylaniline, when all yield the same 7-methylanilino-derivative (forthcoming publication).

The epimeric 7-chloro-benzoates, when treated with diethylaniline at 150°, gave practically identical yields (30%; estimated spectrographically) of 7-dehydrocholesteryl benzoate. It is to be noted that Wintersteiner and Ruigh (*loc. cit.*) found marked differences in the behaviour of the epimeric 7-benzoyloxy-compounds under comparable conditions. The 7-iodo-compounds react with diethylaniline even at room temperature giving products, containing nitrogen but no iodine, the structure of which will be discussed in a subsequent communication.

EXPERIMENTAL.

" β "-7-*Bromocholesteryl Benzoate* (V).—Finely powdered " α "-7-hydroxycholesteryl benzoate (3 g.) suspended in ether (100 c.c.) was treated with phosphorus tribromide (3 g.); the steroid soon went into solution. After 1 hour at room temperature, the product was isolated with ether. Two crystallisations from acetone gave " β "-7-bromocholesteryl benzoate (1·6 g.), m. p. 140° (undepressed on admixture with a sample prepared by the *N*-bromosuccinimide reaction), $[\alpha]_D^{19°}$ − 175° (*c*, 1·05).

" β "-7-*Chlorocholesteryl Benzoate*.—Powered " α "-7-hydroxycholesteryl benzoate (2 g.) (Eckhardt, *loc. cit.*) was added to ether (40 c.c.) and benzene (10 c.c.), followed by phosphorus pentachloride (2 g.) which caused the suspended material to dissolve. After 30 minutes at room temperature, the product was isolated *via* ether and 2 crystallisations from acetone–benzene (4 : 1) gave " β "-7-*chlorocholesteryl benzoate* (1·0 g.), m. p. 149—150°; $[\alpha]_D^{18°}$ − 119° (*c*, 0·52) (Found: C, 77·8; H, 9·4. $C_{34}H_{49}O_2Cl$ requires C, 77·75; H, 9·4%).

" α "-7-*Chlorocholesteryl Benzoate*.—A mixture of thionyl chloride (3 c.c.) and dry pyridine (10 c.c.) was added to a solution of " α "-7-hydroxycholesteryl benzoate (2 g.) in dry pyridine (30 c.c.), both solutions having previously been cooled to 0°. The mixture was kept at 0° for 30 minutes, and was then poured on ice, and extracted with ether. The ethereal extract was washed with dilute acetic acid, water and sodium hydrogen carbonate solution and finally filtered, dried, and evaporated under reduced pressure. The residue was crystallised from acetone–benzene (4 : 1), and recrystallisation from acetone–ethyl acetate (4 : 1) gave " α "-7-*chlorocholesteryl benzoate* (0·44 g.) as plates, m. p. 151°, $[\alpha]_D^{20°}$ + 60·7° (*c*, 0·91) (Found: C, 77·85; H, 9·1%).

" β "-7-*Chlorocholesteryl Acetate* (IX).—Thionyl chloride (0·5 c.c.) was added to a solution of " β "-7-hydroxycholesteryl acetate (500 mg.; see Part XLIX) in dry ether (25 c.c.) at 0° and the mixture was then kept at 20° for 1 hour. Removal of volatile materials under reduced pressure and 2 crystallisations of the residual solid from dry acetone gave " β "-7-*chlorocholesteryl acetate* (290 mg.) as long needles, m. p. 114°, $[\alpha]_D^{20°}$ − 165° (*c*, 0·87) (Found: C, 75·0; H, 10·2. $C_{29}H_{47}O_2Cl$ requires C, 75·2; H, 10·2%).

" β "-7-*Iodocholesteryl Acetate*.—" β "-7-Bromocholesteryl acetate (5 g.) was dissolved in dry acetone (70 c.c.) by gentle warming. When a solution of sodium iodide (5 g.) in dry acetone (30 c.c.) was added with stirring there was an immediate precipitation of sodium bromide, which was filtered off after 1 minute. The filtrate was then cooled in a carbon dioxide–acetone bath and the resulting crystals were filtered off as soon as crystallisation had ceased, since the iodo-compound decomposes slightly in solution, becoming greenish. Any contact of the iodo-compound with metals (*e.g.*, a nickel spatula) should be avoided, since it causes the product to become greenish-black; a glass spatula was used. The pale yellow iodo-compound (4·2 g.) was dried under reduced pressure and had m. p. 91°. Recrystallisation from acetone gave " β "-7-*iodocholesteryl acetate* (3·65 g.), m. p. 92—93°, $[\alpha]_D^{20°}$ − 365° (*c*, 1·02) (Found: C, 63·3; H, 8·5. $C_{29}H_{47}O_2I$ requires C, 62·8; H, 8·55%).

" β "-7-*Iodocholesteryl Benzoate*.—A solution of sodium iodide (0·5 g.) in dry acetone (7 c.c.) was added to a solution of " β "-7-bromocholesteryl benzoate (0·5 g.) in benzene (3 c.c.), and the mixture was swirled around for 2 minutes. The supernatant liquid was decanted from the inorganic precipitate, which was washed with benzene (1 c.c.). Acetone (8 c.c.) was added and the solution cooled to 0° to induce crystallisation and finally cooled in a carbon dioxide–acetone bath to give the crude iodo-compound (0·48 g.), m. p. 108° (decomp.) (when put in bath at 90°). Dissolution in cold benzene, followed by precipitation with acetone, gave " β "-7-*iodocholesteryl benzoate*, m. p. 115° (decomp.) (when put in bath at 110°), $[\alpha]_D^{17°}$ − 270° (*c*, 0·45) (Found: C, 66·85; H, 8·05. $C_{34}H_{49}O_2I$ requires C, 66·2; H, 8·0%).

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362. *Studies in the Sterol Group. Part XLIX. 7-Substituted Cholesterol Derivatives and their Stereochemistry (Part II). Esters of the Epimeric 7-Hydroxycholesterols.*

By H. B. HENBEST and E. R. H. JONES.

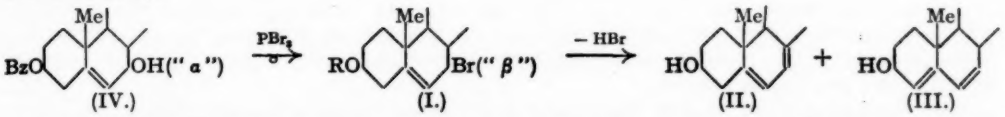
Further evidence for the formulation of the *N*-bromosuccinimide bromination product of cholesteryl acetate as " β "-7-bromocholesteryl acetate (I) has been adduced from the study of replacement reactions of the 7-bromine atom. Partial alkaline hydrolysis leads to the production of the isomeric 7-hydroxy-Δ⁵- and 5-hydroxy-Δ⁶-compounds (XIX and XX), presumably *via* a mesomeric carbonium cation (XVIII). This same intermediate is also apparently involved in certain reactions of the 5-hydroxy-Δ⁶-compounds in which 7-substituted cholesterol derivatives are produced.

The stereochemical picture has been largely completed by the preparation of several new esters of the epimeric " α "- and " β "-7-hydroxycholesterols by these reactions and also by partial acetylation of the 3 : 7-diols (*e.g.*, XXI) and partial hydrolysis of the corresponding diacetates (*e.g.*, XXIII).

WHEN cholesteryl acetate is treated with *N*-bromosuccinimide, a bromo-acetate is produced (Part XLVII, this vol., p. 1783) which has been formulated as " β "-7-bromocholesteryl acetate (I; R = Ac);* analogous compounds are similarly produced by the bromination of cholesteryl

* The significance of the " α " and " β " convention is explained in Part XLVIII.

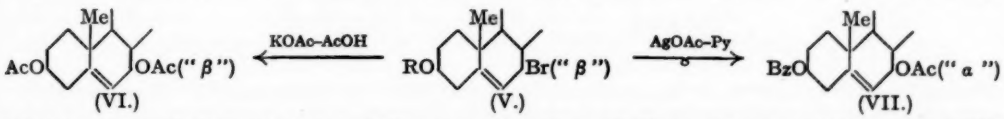
benzoate and cholesteryl chloride. Some evidence in support of the 7-bromo-formulæ for these products has been adduced from the formation of esters of 7-dehydrocholesterol (II) on dehydrobromination with certain tertiary bases, but the value of this evidence is appreciably diminished by the fact that esters of cholesta-4 : 6-dienol (III) are invariably produced simultaneously.



In Part XLVIII (preceding paper) rather more direct proof has been obtained since it has been shown that treatment of the well-authenticated " α "-7-hydroxy-benzoate (IV) (Eckhardt, *Ber.*, 1938, **71**, 469) with phosphorus tribromide in ether yields a bromo-compound (I; R = Bz) identical with that produced by the *N*-bromosuccinimide reaction.

It seemed possible that further useful evidence for the formulation of these bromination products as belonging to the " β "-7-bromo-series would be forthcoming from a study of replacement reactions of the labile bromine atom. Moreover, the preparation of a variety of 7-substituted cholesterol derivatives in this and in other ways was of considerable interest and offered the possibility of amplifying and consolidating the general statement made in Part XLVIII that the " α "-7-substituted cholesterol derivatives are dextrorotatory while those of the " β "-7-series are uniformly lævorotatory.

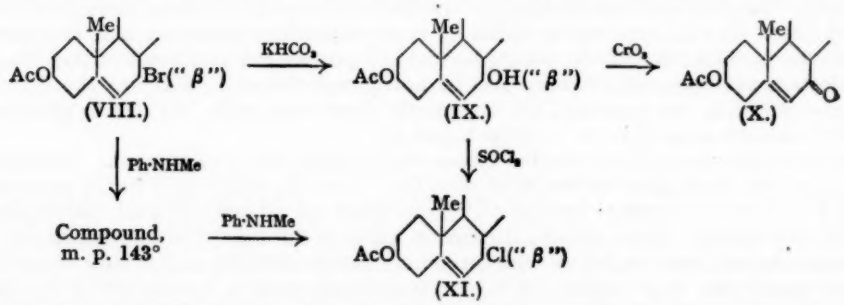
Replacement of the 7-Bromine Atom by Acyloxy-groups.—The 7-bromine atom was readily replaced when the " β "-7-bromo-acetate (V; R = Ac) was treated with potassium acetate in acetic acid at 20°, the main isolable product (30% yield) being the known lævorotatory



" β "-7-acetoxycholesteryl acetate (VI) prepared by Barr, Heilbron, Parry, and Spring (*J.*, 1936, 1437) by acetylation of the " β "-diol. (This diol had been obtained by these authors by hydrolysis of the product resulting from the oxidation of cholesteryl hydrogen phthalate with permanganate.)

The " β "-7-*formoxy*-compound was obtained similarly but in much better yield, and its structure was confirmed by hydrolysis to the " β "-diol. These replacement reactions thus proceed apparently without appreciable inversion of configuration at C_7, but when the " β "-7-bromo-benzoate (V; R = Bz) was treated with silver acetate in pyridine at 20° the main product was the dextrorotatory " α "-7-acetoxycholesteryl benzoate (VII), identical with material made from the " α "-diol by the procedure devised by Eckhardt (*Ber.*, 1938, **71**, 469).

Partial Hydrolysis of " β "-7-Bromo-compounds.—So reactive is the bromine atom in 7-bromo-compounds such as (V; R = Ac or Bz) that selective hydrolysis involving only the bromine atom is possible. With potassium hydrogen carbonate in aqueous dioxan, or better with silver hydroxide in the same medium, the bromo-acetate (VIII) gave a solid product which could not

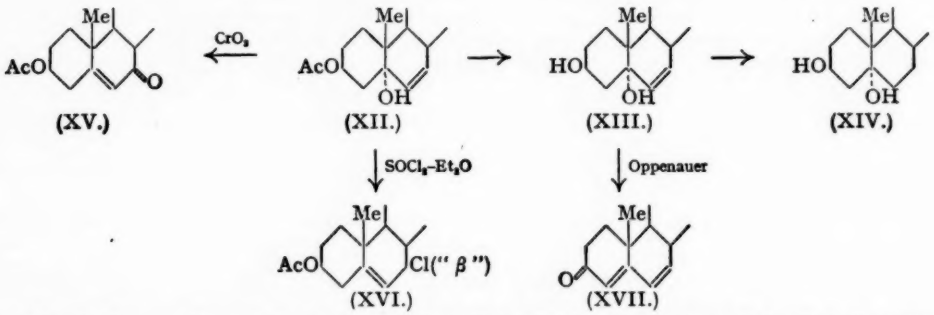


be purified by crystallisation. By chromatography, however, two pure compounds were isolated; one of these (m. p. 143°) is discussed in detail below; the other, lævorotatory like the starting material, was shown to be " β "-7-*hydroxycholesteryl acetate* (IX). Acetylation yielded the known " β "-7-acetoxy-compound, and oxidation with chromic acid produced 7-keto-

cholesteryl acetate (X). Benzoylation gave the hitherto unknown " β "-7-*benzoyloxycholesteryl acetate*. Chlorination with thionyl chloride in ether at 20° gave, as already described in the previous paper, the " β "-7-chloro-acetate (XI), and this was correlated with the corresponding bromo-compound (VIII) by formation of identical products by reaction with methylaniline (forthcoming publication).

Partial hydrolysis of the " β "-7-bromo-benzoate similarly yielded lævorotatory " β "-7-*hydroxycholesteryl benzoate* (benzoylated to the known dibenzoate), together with a second compound (m. p. 175°) corresponding to the second product (m. p. 143°) obtained by hydrolysis of the bromo-acetate.

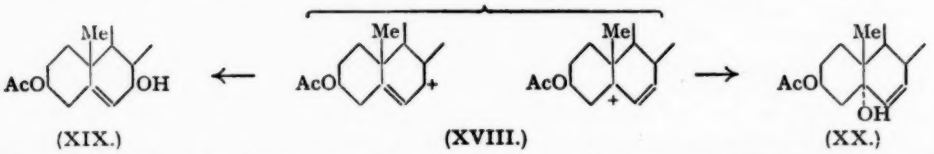
The compound of m. p. 143° was found to be isomeric with the " β "-7-hydroxy-acetate (IX), and it seemed at first that it might be the epimeric and hitherto undescribed " α "-7-hydroxycholesteryl acetate. This was rendered extremely improbable when it proved to be lævorotatory, and quite impossible when it was found that it could neither be acetylated nor benzoylated. Its formulation as 3(β)-*acetoxycholest*-6-*en*-5(α)-*ol* (XII), however, was largely



(XV.) (XII.) (XIII.) (XIV.) (XVI.) (XVII.)

proved by hydrogenation of the corresponding *diol* (XIII) to cholestane-3(β) : 5(α)-diol (XIV), which had been prepared previously by hydrogenation of α-cholesterol oxide (Plattner, Petrzilker, and Lang, *Helv. Chim. Acta*, 1944, **27**, 1872). Benzoylation of the Δ^6-diol (XIII) yielded the product, m. p. 175°, obtained by partial hydrolysis of the " β "-7-bromo-benzoate.

The formation of the isomeric hydroxy-acetates (XIX and XX) by the partial hydrolysis reaction suggests that it proceeds by an S_N1 mechanism (cf. review by Hughes, *J.*, 1946, 974),



(XIX.) (XVIII.) (XX.)

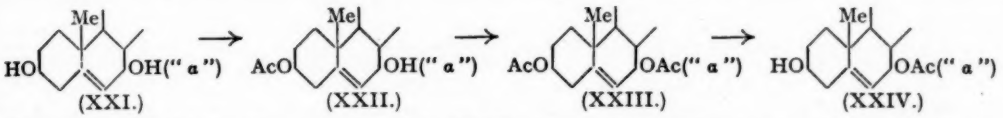
the first stage being the formation of the mesomeric carbonium ion (XVIII) which is then converted into either the 5- or the 7-hydroxy-compound (XIX and XX). On this basis the mechanism of this hydrolysis reaction is closely parallel to that of the elimination reaction which occurs when the 7-bromo-compounds are treated with certain tertiary bases; it has been suggested (Part XLVII) that this is of the E_1 type, separation of the bromide ion leaving the mesomeric carbonium ion (XVIII) which, by loss of a proton, can give rise to either the $\Delta^{5:7}$- or $\Delta^{4:6}$-cholestadienyl acetates. It may also be noted that the diol (XX) has the C_8 hydroxyl group (α)-orientated, the hydroxyl ion apparently combining with (XVIII) to give the more stable *trans*-decalin arrangement of rings A and B.

Some other reactions of the new diol monoacetate (XII) were investigated. Oxidation with chromic acid was slow, much slower than with the 7-hydroxy-compound, but it gave the same product, *viz.*, 7-ketocholesteryl acetate (XV), doubtless *via* an acid-induced rearrangement to the 7-hydroxy-isomer. With thionyl chloride in ether at 20° " β "-7-chlorocholesteryl acetate (XVI) was obtained, presumably *via* the carbonium cation (XVIII), and it may be pointed out that once again the more stable " β "-7-halogeno-compound is formed (cf. Part XLVIII, preceding paper). As was anticipated, Oppenauer oxidation of the diol (XIII) yielded cholesta-4 : 6-dienone, isolated as its semicarbazone.

Only two cholest-6-ene-3(β) : 5-diols, differing in configuration at C_5 (*i.e.*, α and β), can possibly exist, and two such " diols " are already described in the literature. The reactions described for

these two substances are consistent with the formulations suggested, but for neither has any rigorous structural proof been obtained, for example, by hydrogenation. The structures of these two compounds have now been completely elucidated, and this work is described in Part L (following paper).

Partial Acetylation of " α "-7-Hydroxycholesterol and Partial Hydrolysis of the " α "- and " β "-7-Acetoxycholesteryl Acetates.—Various experiments have been carried out in order to prepare 7-hydroxycholesterol derivatives required to complete the series of stereoisomers. Monobenzoylation of " α "-7-hydroxycholesterol (XXI) with benzoic anhydride in pyridine gives a good yield of the 3-monobenzoate (Eckhardt, *loc. cit.*), but, when acetylation of the same diol with the theoretical amount of acetic anhydride in pyridine solution was attempted, only a 5% yield of " α "-7-*hydroxycholesteryl acetate* (XXII) was obtained. This yield could doubtless be improved by using chromatographic methods rather than crystallisation to isolate the monoacetate. [Other workers have experienced difficulty in effecting partial acetylation at the C_3 position (Reichstein and Sorken, *Helv. Chim. Acta*, 1942, **25**, 797; Plattner and Heusser,



ibid., 1944, **27**, 748.] The structure of (XXII) was confirmed by its smooth oxidation to 7-ketocholesteryl acetate (XV) and by acetylation to the known diacetate (XXIII).

Wintersteiner and Ruigh (*J. Amer. Chem. Soc.*, 1942, **64**, 1177, 2453) carried out partial hydrolyses on the epimeric " α "- and " β "-7-benzoyloxycholesteryl benzoates, thus obtaining the two epimeric 7-monobenzoates. The two diacetates (*e.g.*, XXIII) have now been partially hydrolysed yielding " α "-7-*acetoxycholesterol* (XXIV) and " β "-7-*acetoxycholesterol* respectively. Benzoylation of the former gave the " α "-7-acetoxycholesteryl benzoate described by Eckhardt (*loc. cit.*) while the latter gave the new " β "-7-*acetoxycholesteryl benzoate.*

In Part XLVII (*loc. cit.*) attention was directed to a recent publication by Buisman, Stevens, and Vliet (*Rec. Trav. chim.*, 1947, **66**, 83) containing " preliminary results " which to a limited extent are identical with those described in this and the preceding two papers. The work of the Dutch authors on the bromination of cholesteryl esters and the subsequent conversion of the brominated products into 7-dehydrocholesterol has already been commented on (*loc. cit.*), and here certain replacement reactions which Buisman *et al.* have reported are discussed. The Dutch workers were unable to isolate pure bromo-compounds from the *N*-bromosuccinimide brominations, and consequently the few experiments which they carried out on the crude products lose much of their significance. By treatment of " α "-7-hydroxycholesteryl benzoate (IV) with phosphorus tribromide they obtained the same bromo-compound (I; R = Bz), m. p. 140° (which we term " β "-7-bromocholesteryl benzoate), as was obtained by us using the same procedure (Part XLVIII) and also by the bromination of cholesteryl benzoate with *N*-bromosuccinimide (Part XLVII). Buisman *et al.* found that during chromatography on alumina this bromo-compound underwent hydrolysis to " β "-7-hydroxycholesteryl benzoate, m. p. 165—166°, identical with one of the products (m. p. 167—168°) reported in this paper as resulting from hydrolysis with potassium hydrogen carbonate in aqueous dioxan. They also describe an isomeric bromo-benzoate (m. p. 132—133°) obtained by treating the " β "-7-hydroxycholesteryl benzoate (above) with phosphorus tribromide. However, in the absence of optical rotation data and evidence from substitution reactions it is by no means certain that this substance is the hitherto undescribed " α "-7-bromocholesteryl benzoate, as Buisman *et al.* claim.

Experimental.

Replacement of the " β "-7-Bromine Atom by Acyloxy-groups.

" β "-7-Acetoxycholesteryl Acetate (VI.).—Potassium acetate (5 g.) was dissolved in acetic acid (200 c.c.) by gentle warming and then cooled to 20°. Powdered " β "-7-bromocholesteryl acetate (9 g.) was added, and the solution was kept at room temperature for 24 hours. The steroid was isolated with ether; recrystallisation from methanol and then from aqueous acetone gave " β "-7-acetoxycholesteryl acetate (2·2 g.), m. p. and mixed m. p. with an authentic sample, 122°; $[\alpha]_D^{18°}$ − 176° (*c*, 0·63) {Barr *et al.*, *J.*, 1936, 1437, give m. p. 121—122°; $[\alpha]_D^{19°}$ − 174·6° (*c*, 0·86)}. A similar yield of the diacetate was obtained by using pyridine acetate instead of potassium acetate.

" β "-7-Formoxycholesteryl Acetate.—Solutions of " β "-7-bromocholesteryl acetate (2 g.) in ether (20 c.c.), and sodium formate (2 g.) in formic acid (20 c.c.), were mixed, and kept at room temperature for 24 hours. Ether was added, and most of the formic acid was removed by washing with water and the last traces with sodium hydrogen carbonate solution. Removal of the ether and two crystallisations

of the residue from methanol gave "β"-7-*formoxycholesteryl acetate* (1·15 g.) as small prisms, m. p. 98°; $[\alpha]_D^{20°}$ − 139° (*c*, 1·07) (Found: C, 76·0; H, 10·2. $C_{30}H_{48}O_4$ requires C, 76·25; H, 10·2%).

Hydrolysis of "β"-7-Formoxycholesteryl Acetate.—A solution of potassium hydroxide (1 g.) in water (5 c.c.) was added to a suspension of "β"-7-formoxycholesteryl acetate (2 g.) in methanol (100 c.c.), and the mixture was refluxed for 1 hour. The steroid rapidly dissolved. Cooling to room temperature gave a product (1·55 g.), m. p. 178°. Recrystallisation from methanol yielded "β"-7-hydroxycholesterol, m. p. (and mixed) 185°; $[\alpha]_D^{17°}$ − 86·6° (*c*, 1·21) {Barr *et. al* (*loc. cit.*) give m. p. 185°, $[\alpha]_D^{19°}$ −86·4° (*c*, 0·98)}. The mother liquor from the reaction mixture was diluted with a little water to precipitate a further quantity of this material, and after this had been removed by filtration the remaining steroid was isolated *via* ether. The product was benzoylated with benzoyl chloride (3 c.c.) in pyridine (10 c.c.) for 48 hours at room temperature. Isolation of the product *via* ether, followed by recrystallisation from acetone, gave "α"-7-benzoyloxycholesteryl benzoate (0·25 g.), m. p. (and mixed m. p.) 172°; $[\alpha]_D^{16°}$ + 97·5° (*c*, 0·93).

"α"-7-*Acetoxycholesteryl Benzoate* (VII).—"β"-7-Bromocholesteryl benzoate (0·5 g.) was added to a solution of silver acetate (1 g.) in dry pyridine (10 c.c.) which was kept at room temperature for 24 hours. Isolation of the steroid *via* ether, followed by 3 crystallisations from methanol–benzene (3 : 1), gave "α"-7-acetoxycholesteryl benzoate (0·17 g.), m. p. (and mixed m. p. with an authentic sample) 153°.

Partial Hydrolysis of "β"-7-Bromocholesteryl Acetate (VIII).—The bromo-acetate (20 g.) dissolved in dioxan (250 c.c.) was stirred vigorously with a solution of potassium hydrogen carbonate (10 g.) in water (50 c.c.) for 20 hours. The product was isolated with ether, and after removal of the last traces of dioxan under reduced pressure the residue (18·5 g.) was dissolved in benzene (100 c.c.) and adsorbed on a 90 × 2·7 cm. column of Birlec alumina. Development with benzene (5·6 l.) gave (after rejection of some gummy material) a solid product which was crystallised from methanol to give long needles of 3(β)-*acetoxycholest*-6-*en*-5(α)-*ol* (XII) (2·8 g.), m. p. 143°; $[\alpha]_D^{20°}$ − 22·1° (*c*, 0·77) (Found: C, 78·4; H, 10·7. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%). Elution with benzene–ether (3 l.; 9 : 1) yielded another solid product, which was crystallised from aqueous methanol to give flat needles of "β"-7-*hydroxycholesteryl acetate* (IX) (3·85 g.), m. p. 139°; $[\alpha]_D^{20°}$ − 87·5° (*c*, 0·73) (Found: C, 78·4; H, 10·8. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%).

Reactions of "β"-7-Hydroxycholesteryl Acetate (IX).

"β"-7-*Acetoxycholesteryl Acetate.*—The hydroxy-acetate (100 mg.) was treated at room temperature for 40 hours with acetic anhydride (1·5 c.c.) in pyridine (3 c.c.). Isolation *via* ether gave "β"-7-acetoxycholesteryl acetate (72 mg.) as needles from aqueous acetone, m. p. (and mixed m. p. with an authentic specimen) 122°.

7-*Ketocholesteryl Acetate* (X).—The hydroxy-acetate (100 mg.) was oxidised with a solution of chromic acid (30 mg.) in acetic acid (6 c.c.) at room temperature during 2 hours. Dilution with water gave 7-ketocholesteryl acetate (76 mg.), m. p. (and mixed m. p. with an authentic sample) 158°. Light absorption: Maximum, 2360 A.; $\epsilon = 13{,}000$.

"β"-7-*Benzoyloxycholesteryl Acetate.*—The hydroxy-acetate (200 mg.) was treated with benzoyl chloride (2 c.c.) and pyridine (5 c.c.) at room temperature for 2 hours. The steroid isolated *via* ether crystallised after being kept in methanol solution at 0° for several days. Two recrystallisations from methanol gave "β"-7-*benzoyloxycholesteryl acetate* (103 mg.) as needles, m. p. 113°; $[\alpha]_D^{20°}$ − 176° (*c*, 0·62) (Found: C, 78·8; H, 9·5. $C_{36}H_{52}O_4$ requires C, 78·8; H, 9·55%).

Partial Hydrolysis of "β"-7-Bromocholesteryl Benzoate.—The bromo-benzoate (4·5 g.) was dissolved in warm dioxan (150 c.c.) and stirred with a solution of potassium hydrogen carbonate (2·5 g.) in water (10 c.c.) for 48 hours at 50°. The product, isolated with ether, was then adsorbed from benzene (25 c.c.) on a 30 × 1·6 cm. column of activated alumina. Development with benzene–ether (1 l.; 9 : 1) gave, after crystallisation from acetone, 3(β)-benzoyloxycholest-6-en-5(α)-ol (1·2 g.), m. p. 175°, undepressed on mixing with a specimen prepared (as described below) by benzoylation of the diol obtained by hydrolysis of the monoacetate.

Elution with ether yielded "β"-7-*hydroxycholesteryl benzoate* (1·85 g.) which separated from acetone as granular prisms, m. p. 167—168°, $[\alpha]_D^{18°}$ − 50·5° (*c*, 1·32) (Found: C, 80·4; H, 9·85. $C_{34}H_{50}O_3$ requires C, 80·6; H, 9·95%). Benzoylation of this hydroxy-benzoate produced "β"-7-benzoyloxycholesteryl benzoate, m. p. (and mixed m. p. with an authentic specimen) 152°.

Reactions of 3(β)-Acetoxycholest-6-en-5(α)-ol (XII).

Cholest-6-*ene*-3(β) : 5(α)-*diol* (XIII).—3(β)-Acetoxycholest-6-en-5(α)-ol (300 mg.) was refluxed in a solution of potassium hydroxide (200 mg.) in methanol (25 c.c.) for 15 minutes. The product obtained by dilution with water was crystallised from methanol to give *cholest*-6-*ene*-3(β) : 5(α)-*diol* (265 mg.), m. p. 181°; $[\alpha]_D^{20°}$ − 16·4° (*c*, 0·67) (Found: C, 80·5; H, 11·4. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%). Benzoylation of the diol (70 mg.) with benzoyl chloride (1 c.c.) and pyridine (2 c.c.) gave, after 2 crystallisations from acetone, 3(β)-*benzoyloxycholest*-6-*en*-5(α)-*ol* (47 mg.) as needles, m. p. 175°; $[\alpha]_D^{20°}$ − 26·2° (*c*, 1·22) (Found: C, 80·5; H, 10·0. $C_{34}H_{50}O_3$ requires C, 80·6; H, 9·95%).

Cholestane-3(β) : 5(α)-*diol*(XIV).—The diol (100 mg.) in alcohol (30 c.c.) was shaken with hydrogen for 4 hours in the presence of platinic oxide (20 mg.). After the catalyst had been filtered off and the solvent removed under reduced pressure, the residual solid, which gave only a very weak Lifschutz test, was crystallised from methanol to give cholestane-3(β) : 5(α)-diol (77 mg.) as felted needles, m. p. 224°; $[\alpha]_D^{19°}$ + 21·2° (*c*, 0·80) {Plattner, Petrzilka, and Lang, *Helv. Chim. Acta*, 1944, **27**, 513, give m. p. 224·5°; $[\alpha]_D$ + 20·6° (*c*, 0·48)}.

Acetylation with acetic anhydride and pyridine at room temperature gave 3(β)-acetoxycholestan-5(α)-ol, m. p. 184°, after one crystallisation from aqueous methanol (Plattner *et al.*, *loc. cit.*, give m. p. 185°).

Oxidation to 7-Ketocholesteryl Acetate (XV).—A solution of 3(β)-acetoxycholest-6-en-5(α)-ol (100 mg.) in acetic acid (3 c.c.) was treated with a solution of chromic acid (30 mg.) in acetic acid (3 c.c.). Oxidation

was slow, and the mixture was left overnight. The steroid was isolated *via* ether, and the product crystallised from methanol to give 7-ketocholesteryl acetate (55 mg.), m. p. (and mixed m. p. with authentic material) 157°. Light absorption: Maximum, 2370 A.; $\epsilon = 13{,}500$.

" β "-7-*Chlorocholesteryl Acetate* (XVI).—3(β)-Acetoxycholest-6-en-5(α)-ol (100 mg.) was dissolved in dry ether (5 c.c.) and cooled to 0°. Thionyl chloride (0·2 c.c.) was added and the solution was allowed to warm up to room temperature during 1 hour. Solvent was removed under reduced pressure and the residue was twice crystallised from dry acetone to give " β "-7-chlorocholesteryl acetate (Part XLVIII, *loc. cit.*) as needles (48 mg.), m. p. (and mixed m. p.) 113—114°.

Oppenauer Oxidation of Cholest-6-ene-3(β) : 5(α)-diol.—A mixture of the diol (200 mg.), freshly sublimed aluminium *tert.*-butoxide (300 mg.), dry benzene (10 c.c.), and dry acetone (5 c.c.) was refluxed for 24 hours. After addition of water the steroid was isolated *via* ether, and the crude gummy product had light absorption (Maxima, 2820 and 2890 A.; $\epsilon = 19{,}500$ and 19,000) which indicated the presence of about 65% of cholesta-4 : 6-dien-3-one (XVII). A light petroleum (b. p. 40—60°) solution of this product was passed through a short column of activated alumina in order to remove hydroxylic impurities, and the eluate (after removal of the solvent under reduced pressure) was treated with semicarbazide acetate. The crude semicarbazone so obtained was crystallised from methanol to give cholesta-4 : 6-dien-3-one semicarbazone (88 mg.), m. p. (and mixed m. p. with an authentic sample) 235—236° (decomp.). Light absorption: Maximum, 3040 A.; $\epsilon = 35{,}000$. (Wintersteiner and Ruigh, *J. Amer. Chem. Soc.*, 1942, **64**, 2453, give for the light absorption in dioxan: Maximum, 3050 A.; $\epsilon = 46{,}000$.)

Preparation and Reactions of " α "-7-Hydroxycholesteryl Acetate (XXII).

" α "-7-*Hydroxycholesteryl Acetate* (XXII).—" α "-7-Hydroxycholesterol (10 g.; Windaus, Lettré, and Schenck, *loc. cit.*) was dissolved in dry pyridine (40 c.c.) by gentle warming, and the solution was then cooled to 0°. Acetic anhydride (2·5 g.) and dry pyridine (10 c.c.) were added during 5 minutes at 0°, and the mixture was kept at 0° for 4 days after which the steroid was isolated *via* ether. The gelatinous residue was stirred with warm light petroleum (200 c.c.; b. p. 40—60°) and filtered from unchanged diol (5·2 g.). After evaporation of the solvent under reduced pressure, the residue was dissolved in acetic acid (100 c.c.) by gentle warming and then cooled to 10°. The crystalline product (m. p. 97°) was twice crystallised from methanol–water (9 : 1) to give " α "-7-*hydroxycholesteryl acetate* (0·53 g.) as fine filamentous needles, m. p. 110—111°; $[\alpha]_D^{16°} - 5{\cdot}0°$ (*c*, 1·0), or as plates from light petroleum (b. p. 40—60°) (Found: C, 78·05; H, 10·75. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%). Further acetylation with acetic anhydride and pyridine at room temperature gave " α "-7-acetoxycholesteryl acetate (XXIII), m. p. (and mixed m. p. with an authentic sample) 100°.

[Throughout this work the lower-melting form of this diacetate was always obtained. Windaus and Schenck (U.S.P. 2,098,985) state that the two forms have m. p.s 98—100° and 106·5—107·5°.] The hydroxy-acetate (100 mg.) was treated with benzoyl chloride and pyridine at room temperature for 2 hours. Isolation with ether, followed by crystallisation from methanol–benzene (4 : 1), gave long needles of " α "-7-*benzoyloxycholesteryl acetate* (81 mg.), m. p. 166°; $[\alpha]_D^{17°} + 82°$ (*c*, 0·86) (Found: C, 79·2; H, 9·55. $C_{36}H_{52}O_4$ requires C, 78·8; H, 9·55%).

7-*Ketocholesteryl Acetate* (XV).—" α "-7-Hydroxycholesteryl acetate (50 mg.) was suspended in acetic acid (3 c.c.); a solution of chromic acid (30 mg.) in acetic acid (3 c.c.) was added, and gentle warming rapidly completed the reaction. Dilution with water, followed by crystallisation from acetone–methanol, gave 7-ketocholesteryl acetate (32 mg.), m. p. (and mixed m. p. with an authentic sample) 158°.

Partial Hydrolyses of the " α "- and " β "-7-Acetoxycholesteryl Acetates.

" α "-7-*Acetoxycholesterol* (XXIV).—11·2 C.c. of a solution of potassium hydroxide (2·8 g.) in ethanol (250 c.c.) were added to a solution of " α "-7-acetoxycholesteryl acetate (1·1 g.; prepared by acetylation of " α "-7-hydroxycholesterol; Windaus, Lettré, and Schenck, *loc. cit.*) in benzene (5 c.c.) and ethanol (10 c.c.), and the mixture was kept at room temperature for 72 hours. Isolation with ether followed by 2 crystallisations from aqueous methanol gave " α "-7-*acetoxycholesterol* (0·62 g.) as fluffy needles, m. p. 83—84°; $[\alpha]_D^{19°} + 72{\cdot}5°$ (*c*, 1·07) (Found: C, 78·0; H, 10·7. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%).

Benzoylation of this product gave " α "-7-acetoxycholesteryl benzoate, m. p. (and mixed m. p.) 153°. (Sample prepared by the method of Eckhardt, *loc. cit.*)

" β "-7-*Acetoxycholesterol*.—12·5 C.c. of a solution of potassium hydroxide (2·8 g.) in ethanol (250 c.c.) were added to a solution of " β "-7-acetoxycholesteryl acetate (1·21 g.; prepared from " β "-7-bromocholesteryl acetate and potassium acetate) in benzene (10 c.c.) and ethanol (10 c.c.), and the mixture was kept at room temperature for 72 hours. The steroid isolated *via* ether did not crystallise until a methanol solution was left at 0° for 6 days. Recrystallisation from aqueous methanol gave " β "-7-*acetoxycholesterol* (0·63 g.) as long needles, m. p. 143—144° (softening at 140°); $[\alpha]_D^{17°} -193°$ (*c*, 1·25) (Found: C, 78·6; H, 10·8. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%).

A solution of this compound (200 mg.) in pyridine (3 c.c.) and benzoyl chloride (1 c.c.) was kept at room temperature for 24 hours. Isolation of the steroid *via* ether followed by crystallisation from acetone–methanol (1 : 1) gave " β "-7-*acetoxycholesteryl benzoate* as silky needles, m. p. 132°; $[\alpha]_D^{17°} - 121°$ (*c*, 0·79) (Found: C, 78·85; H, 9·4. $C_{36}H_{52}O_4$ requires C, 78·8; H, 9·55%). An identical acetoxybenzoate, m. p. (and mixed) 132°, was obtained by acetylation of the " β "-7-hydroxycholesteryl benzoate produced (see above) by partial hydrolysis of the " β "-7-bromo-benzoate.

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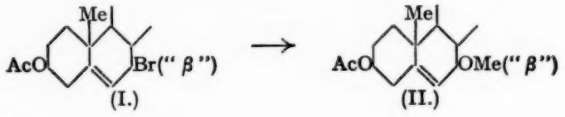
363. *Studies in the Sterol Group. Part L. 7-Substituted Cholesterol Derivatives and their Stereochemistry (Part III). 7-Alkoxycholesterol Derivatives.*

By H. B. Henbest and E. R. H. Jones.

7-Methoxy- and 7-ethoxy-cholesterol derivatives have been prepared from the 7-bromo-compounds. Some of the ethers appear to be formed *via* the " β "-7-hydroxy-compound which has been shown to undergo alkylation very readily in alcoholic solutions in the presence of acids, even acetic acid. As a result of this discovery it has been demonstrated that two compounds hitherto believed to be epimeric cholest-6-ene-3(β) : 5-diols are in fact " β "-7-methoxy- and " β "-7-ethoxy-cholesterols.

The optical rotatory powers of all the known 7-substituted cholesterol derivatives have been collated and discussed.

In continuation of our study of the replacement reactions of 7-halogeno-cholesterol derivatives, it has been found that the introduction of 7-alkoxyl groups by replacement reactions takes place with great ease. Although " β "-7-bromocholesteryl acetate (I) (produced by the action of *N*-bromosuccinimide on cholesteryl acetate; Part XLVII, this vol., p. 1783) reacted rapidly with warm alcohols, only resinous products were obtained. When the bromo-compound was treated with silver nitrate in aqueous dioxan a resinous product was again isolated by ether extraction, but in solution in methyl alcohol this rapidly deposited a crystalline solid which was eventually



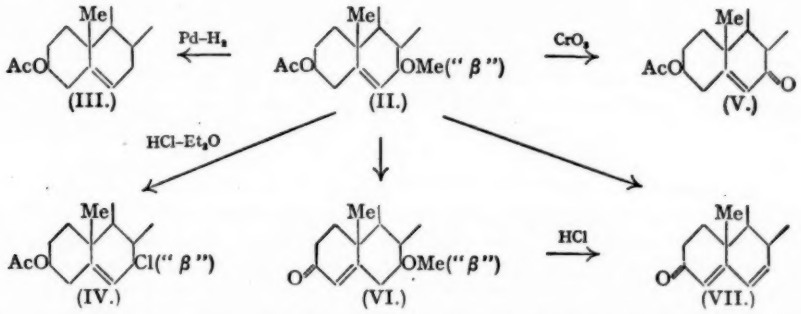
(I.) (II.)

shown to be " β "-7-*methoxycholesteryl acetate* (II), m. p. 111°. The same compound was produced when the 7-bromo-compound was treated with a limited amount of potassium hydroxide in aqueous dioxan, the crude resinous product becoming crystalline on treatment with methyl alcohol. The rôle of the alcohol in these reactions was not immediately obvious; the compound, m. p. 111°, was at first considered to be the then unknown " β "-7-hydroxycholesteryl acetate, and later, 5-hydroxy-3-acetoxycholest-6-ene, when it was discovered that the third oxygen atom could not be esterified. A zero Zerewitinoff value and the absence of any coloration with tetranitromethane rendered even the second choice untenable. These results seemed to indicate a formulation such as 5 : 7-epoxycholestanyl acetate, and it was not until hydrogenation and Oppenauer oxidation experiments had been carried out that the possibility of the presence of an alkoxyl group was seriously considered. Carbon and hydrogen determinations on such substances appear to be unreliable (see below) because of the possibility of methane formation, but a Zeisel determination revealed the methoxyl group. The failure of the tetranitromethane reaction was paralleled by the behaviour of the closely related " α "-7-hydroxycholesterol (Hardegger, Ruzicka, and Stein, *Helv. Chim. Acta*, 1943, **26**, 2220), and this has now been shown to be general with all the 7-hydroxycholesterol derivatives prepared during the course of this work (see preceding papers).

The structure of the methyl ether was confirmed by hydrogenation, oxidation, and other reactions. Hydrogenation in acetic acid solution with a palladium catalyst gave cholesteryl acetate (III) (probably contaminated with a little cholestanyl acetate); similar reductive removal of 7-substituents in cholesterol derivatives (see Part XLVIII, this vol., p. 1788) has been observed by Barr, Heilbron, Parry, and Spring (*J.*, 1936, 1437) and Wintersteiner and Ruigh (*J. Amer. Chem. Soc.*, 1942, **64**, 2453). In the previous cases completely hydrogenated (cholestanol) derivatives were obtained; the isolation of cholesteryl acetate in the present example clearly indicates the sequence of events, the activated 7-substituent being removed before the saturation of the activating ethylenic linkage.

The ether grouping was found to be readily replaced in the presence of acidic reagents; hydrogen chloride in ether yielded " β "-7-chlorocholesteryl acetate (IV), and treatment with acetic acid containing a trace of sulphuric acid gave the corresponding 7-acetoxy-compound. A somewhat analogous reaction ensued when the methoxy-compound was oxidised in acetic acid

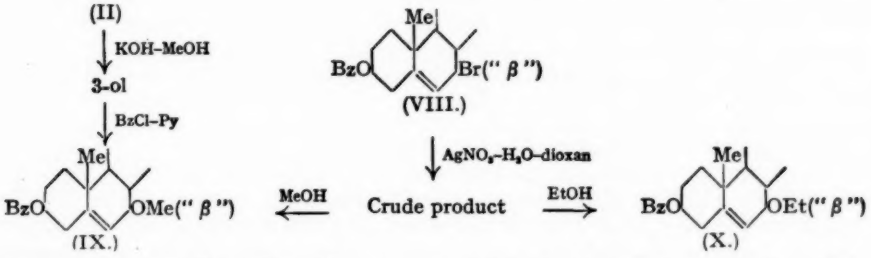
solution with chromic acid; oxidation proceeded only very slowly, but the product was 7-ketocholesteryl acetate (V) :



After this work had been completed a structurally similar unsaturated methoxy-steroid exhibiting closely analogous reactions was described by Kendall and his co-workers (*J. Biol. Chem.*, 1946, **164**, 569). This 12-methoxy-$\Delta^{9:11}$-cholenate readily undergoes methoxyl-group fission with acidic reagents and is slowly oxidised by chromic acid to the 12-keto-compound.

Oxidation of the " β "-7-*methoxycholesterol* under the usual Oppenauer conditions proceeded in the expected manner and gave " β "-7-*methoxycholest-4-en-3-one* (VI) together with some cholesta-4 : 6-dienone (VII). The formation of the dienone from the methoxy-ketone (VI) takes place smoothly under the influence of hydrogen chloride in ethereal solution.

It was thus established that a 7-methoxy-compound had been prepared by the rather unusual procedure employed, *i.e.*, the methoxyl group having been introduced as a result of crystallising the crude product from methanol; the following further experiments led to the elucidation of the reactions involved. The bromo-benzoate (VIII) was mixed with a solution of silver nitrate

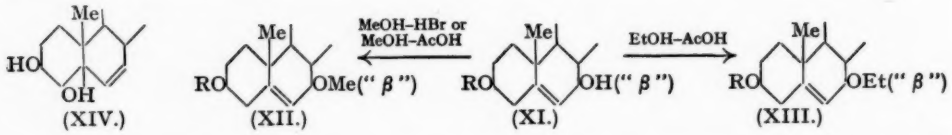


in aqueous dioxan; silver bromide was precipitated almost immediately. When the non-crystalline product, isolated with ether, was treated with methyl alcohol it gave " β "-7-*methoxycholesteryl benzoate* (IX) (identical with the material prepared by benzoylation of the alcohol obtained from the methoxy-acetate). On the other hand, treatment with ethyl alcohol yielded the corresponding " β "-7-*ethoxycholesteryl benzoate* (X). These results suggested the possibility that the crude product was " β "-7-hydroxycholesteryl acetate (XI; R = Ac) and that this intermediate was then etherified by the alcohol in the presence of nitric acid from some 7-nitrate, or hydrogen bromide, the latter being produced from residual bromo-compound which had escaped hydrolysis. This hypothesis was confirmed by the fact that when a solution of " β "-7-hydroxycholesteryl acetate (XI; R = Ac) in methanol was treated with a trace of hydrogen bromide the methoxy-acetate (XII; R = Ac) soon crystallised out.

Further confirmation of the hypothesis was forthcoming from experiments in which " β "-7-hydroxycholesterol (XI; R = H) was subjected to the action of alcohols in the presence of acetic acid as the acidic catalyst. With methyl alcohol " β "-7-methoxycholesterol (XII; R = H) was obtained, whereas the use of ethyl alcohol gave " β "-7-*ethoxycholesterol* (XIII; R = H).

In the methyl alcohol experiments a small quantity of an isomeric methyl ether was isolated from the mother liquors as its dextrorotatory benzoate. This is regarded as " α "-7-*methoxycholesteryl benzoate* since the formation of some of the " α "-7-ether would be expected in view of the known tendency of " β "-7-hydroxycholesterol to form an equilibrium mixture with the " α "-isomer under the influence of acetic acid (Ruzicka, Prelog, and Tagmann, *Helv. Chim.*

Acta, 1944, **27**, 1149). Additional evidence for the structure proposed for this isomeric ether was obtained when the derived sterol, "α"-7-*methoxycholesterol*, was oxidised by the Oppenauer method, the light absorption of the crude product indicating the presence of some 30% of an αβ-unsaturated ketone and a similar amount of cholesta-4 : 6-dienone.



It was mentioned in the preceding paper, in which the preparation and complete characterisation of cholest-6-ene-3(β) : 5(α)-diol (XIV) were described, that only two such 3(β)-diols could possibly exist [*i.e.* 5(α) and 5(β)] and that two such diols were already known. As an outcome of our work on the 7-alkoxycholesterol derivatives we have been able to clear up this difficulty by showing that neither of these substances is a diol or even a 3 : 5-dihydroxy-derivative (cf. Henbest and Jones, *Nature*, 1946, **158**, 950).

Wintersteiner and Bergström (*J. Biol. Chem.*, 1941, **141**, 597; 1942, **143**, 503) obtained what they believed to be a cholest-6-ene-3(β) : 5-diol (XIV) by heating under reflux a solution of " β "-7-hydroxycholesterol in ethyl alcohol containing 10% of acetic acid. They observed that their product gave cholesta-4 : 6-dienone on oxidation by the Oppenauer method with aluminium phenoxide, but they were surprised to find that they could not hydrogenate their " diol " to cholestane-3 : 5-diol [a reaction that is readily achieved with the true Δ^6-diol (preceding paper)]. It is now clear that Wintersteiner and Bergström were dealing with " β "-7-ethoxycholesterol, and this has been confirmed by its preparation by their method and also from a 7-bromo-compound. In addition, Dr. Wintersteiner very kindly sent us a sample of the benzoate of his product, and no depression was observed in a mixed m. p. determination.

During the course of their extensive and remarkably thorough investigations on the steroid content of various organ extracts, Prelog, Ruzicka, and Stein (*Helv. Chim. Acta*, 1943, **26**, 2222) isolated a compound from pig spleen which they provisionally formulated as cholest-6-ene-3(β) : 5-diol (XIV). It seemed as if their substance was the 5-epimer of the Wintersteiner and Bergström " diol ", and in agreement with this conception they found that on Oppenauer oxidation (with aluminium phenoxide) cholesta-4 : 6-dienone was formed. The constants of the " diol " and its derivatives obtained by the Swiss workers were observed to be identical with those of our " β "-7-methoxycholesterol and its derivatives, and in mixed m. p. determinations (kindly carried out by Dr. Prelog on the sterol and its acetate and benzoate) no depressions were oberved. Carbon and hydrogen determinations on these alkoxy-sterols and their derivatives are unreliable unless special precautions are taken, and this doubtless explains why both the Swiss and the American workers were led to draw incorrect deductions as to the structures of their compounds.

It is practically certain that the " β "-7-methoxycholesterol isolated by Prelog, Ruzicka, and Stein (*loc. cit.*) was not present in the original organ extract. One of the stages in the treatment of the pig-spleen material involved the separation of ketonic from non-ketonic substances by means of the Girard reagent which was used in methyl-alcoholic solution containing acetic acid. As has already been mentioned, under these conditions " β "-7-hydroxycholesterol, which is known to occur in animal tissues (Wintersteiner and Ritzmann, *J. Biol. Chem.*, 1940, **136**, 697; Hardegger, Ruzicka, and Tagmann, *Helv. Chim. Acta*, 1943, **26**, 2205), would be converted into the 7-methoxy-compound. This has been shown to be so in the presence or absence of the Girard reagent. The conclusion that the methoxycholesterol was an artefact is further strengthened by the fact that in the two cases cited above, where the " β "-7-hydroxycholesterol was isolated from natural sources, the Girard separation was not employed, the diol being isolated directly by chromatographic methods.

A 7-phenyl ether was obtained by interaction of " β "-7-bromocholesteryl acetate and potassium phenoxide in methyl alcohol, the product, formed presumably as the result of an inversion at C_7, being the dextrorotatory " α "-7-*phenoxycholesteryl acetate*.

The optical rotatory powers of all the known 7-substituted cholesterol derivatives (with the exception of certain amino-compounds which will be discussed in a later publication) are given in Table I.

In the steroid series, optical rotation differences between epimers are usually small, and Table I further emphasises the point (see Part XLVIII, *loc. cit.*) that for 7-epimers in the

cholesterol series these differences are remarkably large, sufficiently and so consistently large as to justify the conclusion (see Part XLVIII, *loc. cit.*) that sign of rotation can be used to assign compounds to the " α "- or the " β "-series.

The use of the method of molecular rotation differences in the steroid series has proved of value in relation to certain structural problems (Barton, *J.*, 1945, 813; 1946, 512, 1116). This method has been used in order to compare the 7-substituted cholest-5-enols described in this and previous papers with the unsubstituted Δ^5-stenols. The molecular rotation differences

TABLE I.

Optical rotatory powers ($[\alpha]_D$) *of 7-substituted cholesterol derivatives.*

	Cholesterol. −26°.		Cholesteryl acetate. −43°.		Cholesteryl benzoate. −17°.	
	" α."	" β."	" α."	" β."	" α."	" β."
7-Hydroxy-	+ 7°	− 87°	− 5°	− 88°	+ 14°	− 51°
7-Acetoxy-	+ 73	−193	+52	−176	+ 76	−121
7-Benzoyloxy-	+111	−201	+82	−176	+ 94	−106
7-Methoxy-	+ 23	−127	+18	−124	+ 39	− 34
7-Chloro-	—	—	—	−165	+ 61	−119
7-Bromo	—	—	—	−245	—	−172
7-Iodo-	—	—	—	−362	—	−270
7-Phenoxy-	+111	—	+83	—	+114	—

(M.R.D.) are given in Table II where Δ_1 is the M.R.D. between the 3(β)-sterol and its 3-acetate and Δ_2 is the M.R.D. between the sterol and its benzoate, and these values are compared with the standard values. Only the Δ_1 and Δ_2 values of the hydroxy- and methoxy-compounds approximate to the differences for the unsubstituted compounds, large deviations being apparent in all the other cases. These deviations are attributable in part to the size of the C_7 substituents, but also to the polarisable nature of the groups associated with the anomalies. Barton and Cox (*Nature*, 1947, **159**, 470) have shown that acetyl, benzoyl, and other groups, even in the 17-position, can cause anomalies in M.R.D.s for the 3-position.

TABLE II.

Molecular rotation differences for 7-substituted cholesterol derivatives.

	Δ_1 (× 10^{-2}) ($[M]_D$ of 3-acetate − $[M]_D$ of 3-ol).	Δ_2 (× 10^{-2}) ($[M]_D$ of 3-benzoate − $[M]_D$ of 3-ol).
" α "-7-Hydroxy-	− 38°	+ 54°
" β "-7-Hydroxy-	− 41	+ 92
" α "-7-Acetoxy-	− 72	+ 92
" β "-7-Acetoxy-	+ 2	−195
" α "-7-Benzoyloxy-	−113	+ 48
" β "-7-Benzoyloxy-	+ 54	+372
" α "-7-Methoxy-	− 12	+106
" β "-7-Methoxy-	− 39	+ 92
" α "-7-Phenoxy-	−100	+132
Average values for Δ^5-stenols (Barton and Cox, *loc. cit.*)...	− 34	+ 80

EXPERIMENTAL.

" β "-7-*Methoxycholesteryl Acetate* (II).—(*a*) A solution of silver nitrate (7·5 g.) in water (50 c.c.) was added all at once with stirring to a solution of " β "-7-bromocholesteryl acetate (15 g.) in dioxan (200 c.c.). There was an immediate precipitation of silver bromide. After 5 minutes, ether (500 c.c.) was added, and the ethereal solution was then decanted from the silver salts, washed with distilled water, and dried (Na_2SO_4). After the ether had been removed under reduced pressure, the residue was dissolved in methanol (150 c.c.) and water (5 c.c.) and left overnight. The crystalline product which separated from the strongly acidic solution was recrystallised from acetone to give a product (7·6 g.), m. p. 109°. Further recrystallisation from acetone or acetone–methanol (1 : 1) gave " β "-7-*methoxycholesteryl acetate* as rectangular needles, m. p. 111°, $[\alpha]_D^{20°}$ − 124° (*c*, 1·05) (Found: C, 78·35; H, 10·8; OMe, 6·4. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0; OMe, 6·75%). {Prelog, Ruzicka, and Stein, *loc. cit.* give m. p. 110—111°, $[\alpha]_D^{20°}$ − 118° (*c*, 0·56) for this compound, which they suggested might be the 3-acetate of cholest-6-ene-3(β) : 5-diol.}

(*b*) A solution of " β "-7-bromocholesteryl acetate (3 g.) in ether (30 c.c.) was added to a solution of potassium hydroxide (0·34 g.) in methanol (30 c.c.). Potassium bromide soon began to separate, and after the mixture had been kept at 25° for 15 minutes, the steroid was isolated with ether. Two recrystallisations from methanol gave slightly impure " β "-7-methoxycholesteryl acetate (1·4 g.), m. p. 109°, undepressed on admixture with a specimen prepared as in (*a*). A similar yield of the methoxy-compound was obtained by substitution of potassium benzoate for the potassium hydroxide. The yield in either case was somewhat improved (1·7 g.) by filtering a light petroleum (b. p. 40—60°)

solution of the crude product through a short column of activated alumina, followed by crystallisation from methanol.

" β "-7-*Methoxycholesterol and* " β "-7-*Methoxycholesteryl Benzoate* (IX).—(*a*) " β "-7-Methoxycholesteryl acetate (1 g.) was refluxed in methanol solution (50 c.c.) containing potassium hydroxide (0·5 g.) for 30 minutes. Water (5 c.c.) was then added, and on cooling, 0·91 g. of product, m. p. 158°, was deposited. Recrystallisation from methanol gave " β "-7-*methoxycholesterol* (0·85 g.) in long needles, m. p. 158—159°, $[\alpha]_D^{20°}$ − 127° (*c*, 0·79) (Found: C, 80·4; H, 11·5. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%) {Prelog, Ruzicka, and Stein,* *loc. cit.*, give m. p. 156°, $[\alpha]_D^{19°}$ − 132° (*c*, 0·59)}.

Benzoylation of this product with benzoyl chloride in pyridine in the usual manner gave " β "-7-*methoxycholesteryl benzoate* as needles from acetone, m. p. 136°, $[\alpha]_D^{20°}$ − 84·3° (*c*, 0·83) (Found: C, 80·6; H, 10·1. $C_{35}H_{52}O_3$ requires C, 80·7; H, 10·1%) {Prelog, Ruzicka, and Stein,* *loc. cit.*, give m. p. 134—135°, $[\alpha]_D^{20}$ − 79° (*c*, 0·68)}.

When a solution of silver nitrate (150 mg.) in water (1 c.c.) was added to a solution of " β "-7-bromocholesteryl benzoate (150 mg.) in dioxan (7·5 c.c.), there was an immediate precipitation of silver bromide. After 2 minutes ether was added, and the solution was decanted from silver bromide, dried (Na_2SO_4), and evaporated under reduced pressure. The residual gum was dissolved in warm methanol; this solution soon deposited solid material which after two recrystallisations from acetone gave " β "-7-methoxycholesteryl benzoate (56 mg.), m. p. (and mixed m. p.) 135°.

(*b*) A solution of " β "-7-hydroxycholesterol (2 g.) in methanol (90 c.c.) and acetic acid (10 c.c.) was heated under reflux for 5 hours. The steroid was isolated *via* ether, and after 3 crystallisations gave long needles of " β "-7-methoxycholesterol (0·64 g.), m. p. 158°, undepressed on admixture with a specimen prepared by method (*a*). (Benzoylation gave " β "-7-methoxcholesteryl benzoate, m. p. and mixed m. p. 136°.) The mother liquor from the first crystallisation (above) was diluted with water, and the steroid isolated *via* ether. This product was treated with benzoyl chloride in pyridine at room temperature; isolation *via* ether followed by two crystallisations from acetone–benzene (3 : 1) gave " α "-7-*methoxycholesteryl benzoate* (0·35 g.), m. p. 151°, $[\alpha]_D^{16°}$ + 38·6° (*c*, 1·15) (Found: C, 80·9; H, 10·1; OMe, 6·3. $C_{35}H_{52}O_3$ requires C, 80·7; H, 10·1; OMe, 6·0%).

" α "-7-*Methoxycholesterol.*—" α "-7-Methoxycholesteryl benzoate (280 mg.) in benzene (5 c.c.) was refluxed with a solution of potassium hydroxide (100 mg.) in ethanol (5 c.c.) for 4 hours. Isolation in the usual way gave " α "-7-*methoxycholesterol* (125 mg.) as long needles after two crystallisations from aqueous methanol, m. p. 146—147°, $[\alpha]_D^{16°}$ + 22·9° (*c*, 0·87) (Found: C, 80·4; H, 11·5. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%). Acetylation of the sterol with acetic anhydride in pyridine gave " α "-7-*methoxycholesteryl acetate* as needles from methanol, m. p. 93—94°, $[\alpha]_D^{16°}$ + 18·2° (*c*, 1·20) (Found: C, 78·5; H, 10·8. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%).

Oppenauer oxidation of " α "-7-methoxycholesterol with acetone in the presence of aluminium *tert.*-butoxide gave a gum, with the following light absorption: Maximum, 2450 A.; ε = 5000 corresponding to about 30% of " α "-7-methoxycholest-4-en-3-one. Maximum: 2810 A.; ε = 9000 corresponding to about 30% of cholesta-4 : 6-dien-3-one.

" β "-7-*Ethoxycholesterol* (XIII; R = H).—This compound was prepared from " β "-7-hydroxycholesterol by using the procedure of Bergström and Wintersteiner (*loc. cit.*). The " β "-7-*ethoxycholesterol* crystallised from methanol in small plates, m. p. 138°, $[\alpha]_D^{15°}$ − 132° (*c*, 1·27) (Found: C, 81·0; H, 11·85; OEt, 10·1. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7; OEt, 10·45%). {Bergström and Wintersteiner give m. p. 139–140°, $[\alpha]_D^{24°}$ − 134°, for this compound, which they believed to be cholest-6-ene-3(β) : 5-diol.}

" β "-7-*Ethoxycholesteryl Benzoate* (X).—The preparation of the 7-methoxy-benzoate from the bromo-compound, described above, was repeated except that the crude gum was dissolved in ethanol instead of methanol. Two recrystallisations from ethanol gave " β "-7-*ethoxycholesteryl benzoate* (25 mg.), m. p. 116°, undepressed on admixture with a sample prepared by Bergström and Wintersteiner (*J. Biol. Chem.*, 1941, **141**, 597), $[\alpha]_D^{17°}$ − 88·0° (*c*, 1·00). Bergström and Wintersteiner describe this compound as the 3-monobenzoate of cholest-6-ene-3(β) : 5-diol, but their analytical data are in excellent agreement with the " β "-7-ethoxycholesteryl benzoate formulation.

" β "-7-*Chlorocholesteryl Acetate* (IV).—" β "-7-Methoxycholesteryl acetate (250 mg.) was dissolved in ethereal hydrogen chloride (10 c.c.; half-saturated solution) at 0°, and kept at 0° overnight. After removal of the solvent under reduced pressure, the residue was twice recrystallised from dry acetone to give " β "-7-chlorocholesteryl acetate (95 mg.), m. p. 114°, undepressed on admixture with the product, m. p. 114°, obtained from " β "-7-hydroxycholesteryl acetate by treatment with thionyl chloride.

" β "-7-*Acetoxycholesteryl Acetate.*—The 7-methoxy-compound (250 mg.) was dissolved in acetic acid (20 c.c.) and cooled to 10°. Acetic acid (5 c.c.) containing 1 drop of concentrated sulphuric acid was added, and the solution kept at 10° for 5 minutes. Isolation of the steroid *via* ether gave a gum that solidified in contact with methanol. Crystallisation from methanol gave " β "-7-acetoxycholesteryl acetate (105 mg.), m. p. 122°, undepressed on admixture with an authentic sample. Hydrolysis and subsequent benzoylation of the diacetate gave " β "-7-benzoyloxycholesteryl benzoate, m. p. 152°, undepressed on admixture with an authentic sample.

7-*Ketocholesteryl Acetate* (V).—A solution of " β "-7-methoxycholesteryl acetate (300 mg.) in acetic acid (10 c.c.) containing chromic acid (100 mg.) was kept at room temperature for 24 hours. The steroid was then isolated with ether, and the solid product, dissolved in light petroleum (b. p. 40—60°), chromatographed on an 18 × 1·2 cm. column of activated alumina. The eluate obtained by development with light petroleum (b. p. 40—60°) contained unchanged starting material (105 mg.). Development with benzene, evaporation, and two crystallisations of the residual solid from acetone gave 7-ketocholesteryl acetate (95 mg.), m. p. 157—158°, undepressed on admixture with an authentic sample.

Hydrogenation of " β "-7-*Methoxycholesteryl Acetate.*—A solution of the methoxy-acetate (1 g.) in " AnalaR " acetic acid (50 c.c.) was shaken with hydrogen and freshly prepared palladium black (100 mg.); after 18 hours, 64 c.c. (1·2 mols.) of hydrogen had been absorbed. The steroid was isolated

* These authors believed these compounds might be cholest-6-ene-3-(β) : 5-diol and its 3-monobenzoate respectively.

with ether, and the semi-solid product was chromatographed on a 30 × 1·6 cm. column of activated alumina, the chromatogram being developed with light petroleum (b. p. 40—60°) and the eluate collected in 50 c.c. portions. The first two fractions gave a small amount of gum; fractions 3 and 4 yielded material (0·58 g.) of m. p. 111—112°, $[\alpha]_D^{20°}$ − 38·9° (*c*, 0·46), after one crystallisation from acetone–methanol (1 : 1), which was not altered by further recrystallisation. It gave a yellow colour with tetranitromethane, and was subsequently identified as impure cholesteryl acetate (m. p. 114°, $[\alpha]_D^{20°}$ − 42·5°), probably contaminated with some cholestanyl acetate {m. p. 110—111°, $[\alpha]_D^{20°}$ − 13·5° (*c*, 0·89)}, since by hydrolysis and crystallisation it yielded pure cholesterol.

" β "-7-*Methoxycholest*-4-*en*-3-*one* (VI).—A mixture of " β "-7-methoxycholesterol (3·5 g.), freshly sublimed aluminium *tert.*-butoxide (3 g.), dry benzene (70 c.c.), and dry acetone (40 c.c.) was gently refluxed for 24 hours with the exclusion of moisture. After addition of water, the steroid was isolated with ether. Most of the mesityl oxide present was removed in a high vacuum, the last traces being removed by adding a little xylene and again evaporating in a high vacuum. The resulting gum gave the following light absorption data: Maximum, 2420 A.; $\epsilon = 9500$, corresponding to about 55% of " β "-7-methoxycholest-4-en-3-one. Maxima, 2810 and 2900 A.; $\epsilon = 9500$ and 8500 respectively, corresponding to about 35% of cholesta-4 : 6-dien-3-one. The gum was dissolved in a mixture of acetone (10 c.c.) and methanol (30 c.c.), and scratched to induce crystallisation. The crude solid (m. p. *ca.* 125°) was twice crystallised from acetone–methanol (1 : 1) to give " β "-7-*methoxycholest*-4-*en*-3-*one* (1·15 g.) in small prisms, m. p. 143°, $[\alpha]_D^{20°}$ + 38·3° (*c*, 1·22) (Found: C, 80·95; H, 11·2. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%). Light absorption: Maximum, 2420 A.; $\epsilon = 16{,}000$ (Jones and Wilkinson, *J.*, 1942, 391, for cholest-4-en-3-one give maximum, 2405 A.; $\epsilon = 18{,}000$).

The 2 : 4-*dinitrophenylhydrazone* crystallised from benzene–alcohol (1 : 1) in vermilion needles, m. p. 196° (Found: C, 68·2; H, 8·2; N, 9·05. $C_{34}H_{50}O_5N_4$ requires C, 68·6; H, 8·5; N, 9·4%). Light absorption: Maximum, 3950 A.; $\epsilon = 31{,}000$ (Jones and Wilkinson, *loc. cit.*, for cholest-4-enone 2 : 4-dinitrophenylhydrazone give maximum, 3910 A.; $\epsilon = 32{,}000$).

Cholesta-4 : 6-*dien*-3-*one* (VII) *from* " β "-7-*Methoxycholest*-4-*en*-3-*one* (VI).—The ketone (100 mg.) was dissolved in half-saturated ethereal hydrogen chloride (5 c.c.) and kept overnight at room temperature. The solvent was removed under reduced pressure, and the residue was twice crystallised from methanol–acetone (3 : 1) to give cholesta-4 : 6-dien-3-one (52 mg.), m. p. and mixed m. p. 81°, $[\alpha]_D^{16°}$ + 37° (*c*, 1·07). Light absorption: Maxima, 2810 A. and 2900 A.; $\epsilon = 28{,}000$ in each case (Wintersteiner and Ruigh, *J. Amer. Chem. Soc.*, 1942, **64**, 2453, give maximum, 2850 A.; $\epsilon = 26{,}000$).

" β "-7-*Methoxycoprostan*-3-*one*.—" β "-7-Methoxycholest-4-en-3-one (500 mg.) dissolved in ethyl acetate (40 c.c.) was shaken with hydrogen and freshly prepared palladium black (50 mg.); approximately 1 mol. of hydrogen (28 c.c.) was absorbed within 15 minutes. The catalyst was filtered off, and the solvent removed under reduced pressure; the residual gum solidified in contact with acetone. Two recrystallisations from aqueous acetone (the product tended at first to form an emulsion) gave " β "-7-*methoxycoprostan*-3-*one* (310 mg.), m. p. 72—73°, $[\alpha]_D^{21°}$ + 22·7° (*c*, 1·03) (Found: C, 80·45; H, 11·3. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%). A further quantity (95 mg.), m. p. 71—72°, was obtained from the mother liquors.

" β "-7-Methoxycoprostan-3-one was recovered unchanged after being left in ethereal hydrogen chloride solution overnight (compare " β "-7-methoxycholest-4-en-3-one).

The ketone readily gave a 2 : 4-*dinitrophenylhydrazone* which separated from alcohol–benzene (3 : 1) as yellow leaflets, m. p. 158—159° (Found: C, 68·4; H, 8·75. $C_{34}H_{52}O_5N_4$ requires C, 68·4; H, 8·8%). Light absorption: Maximum, 3660 A.; $\epsilon = 26{,}500$.

" α "-7-*Phenoxycholesteryl Acetate*.—" β "-7-Bromocholesteryl acetate (2 g.) dissolved in ether (20 c.c.) was added to a solution of phenol (2 g.) and potassium hydroxide (0·5 g.) in methanol (20 c.c.). The mixture was kept at 25° for 30 minutes, and the steroid was then isolated with ether, excess of phenol being removed by dilute aqueous sodium hydroxide solution. Crystallisation from acetone and then from acetone–methanol (3 : 1) gave " α "-7-*phenoxycholesteryl acetate* (1·03 g.) as fine matted needles, m. p. 154°, $[\alpha]_D^{20°}$ + 83° (*c*, 0·77) (Found: C, 80·8; H, 10·2. $C_{35}H_{52}O_3$ requires C, 80·7; H, 10·1%). Light absorption: Maximum, 2240 A.; $\epsilon = 15{,}500$.

" α "-7-*Phenoxycholesterol*.—The acetate (1·1 g.) was dissolved in hot methanol (50 c.c.) and the least amount of benzene necessary to effect complete solution; potassium hydroxide (0·5 g.) in a little water was added, and the solution was refluxed for 15 minutes. The product (m. p. 139°) crystallised on cooling; recrystallisation from methanol containing a little ether gave " α "-7-*phenoxycholesterol* (0·88 g.) as micro-needles, m. p. 140°, $[\alpha]_D^{20°}$ + 111° (*c*, 0·53) (Found: C, 82·8; H, 10·25. $C_{33}H_{50}O_2$ requires C, 82·8; H, 10·5%). Benzoylation of this sterol gave " α "-7-*phenoxycholesteryl benzoate* as needles from acetone–benzene (4 : 1), m. p. 167° (clearing at 177°), $[\alpha]_D^{18°}$ + 114° (*c*, 0·72) (Found: C, 82·6; H, 9·1. $C_{40}H_{54}O_3$ requires C, 82·45; H, 9·35%).

The authors wish to thank Dr. O. Wintersteiner for a sample of the benzoate of " β "-7-ethoxycholesterol, and Dr. V. Prelog for kindly carrying out mixed m. p. determinations with the materials isolated from pig spleen.

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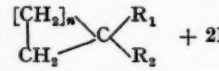
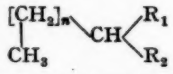
364. *Physical Properties and Chemical Constitution. Part XVIII. Three-membered and Four-membered Carbon Rings.*

By GEORGE H. JEFFERY and ARTHUR I. VOGEL.

New measurements have been made of the refractivities at 20° and the parachors of a number of *cyclo*propane and *cyclo*butane compounds, largely esters of *cyclo*propane- and *cyclo*butane-carboxylic and -1 : 1-dicarboxylic acids. The contributions of the three- and four-membered carbon rings have been computed from the relationship :

Ring constant =  + 2H − 

The necessary physical data for H and the reference compounds are given in the earlier papers of this series. The results are :

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Three-carbon ring	12·3	0·592	0·614	0·656	0·646	−4·72
Four-carbon ring	10·0	0·303	0·317	0·332	0·322	−4·67

The new constants differ appreciably from those previously accepted.

THE early attempts to determine the contribution to the refractivity of the three- and four-membered carbon rings cannot now be regarded as satisfactory for the following reasons: (1) The selection of compounds included many containing dicyclic structures. (2) The calculations were based upon erroneous values for the CH_2 constants (compare Vogel, Part IX, *J.*, 1946, 133). The most comprehensive data are due to Ostling (*J.*, 1912, **101**, 468), whose R_D values for the *cyclo*propane and *cyclo*butane rings were 0·71 and 0·48, respectively (for a detailed review, see Eisenlohr, "Spektrochemie organischer Verbindungen, Molekularrefraktion und -dispersion", Ferdinand Enke, 1912, 89—91, 134—141). The parachor contribution of the three-membered ring is based upon data on 9 compounds of very varied type which include ethylene oxide and epichlorohydrin and upon a CH_2 value of 39·0 (compare Vogel, Part IX, who found 40·0); the extreme values were 12·9 and 20·2 and the mean was 16·7 (Sugden and Wilkins, *J.*, 1927, 240). The constant of the four-membered ring was computed from the results upon ethyl 1-cyano*cyclo*butane-1-carboxylate, ethyl *cyclo*butane-1 : 1-dicarboxylate, and ethyl *cyclo*butanecarboxylate and was given as 11·6 (Sugden and Wilkins, *J.*, 1927, 141).

We have determined the parachors and refractivities of 10 simple *cyclo*propane compounds (largely esters of *cyclo*propane-carboxylic and 1 : 1-dicarboxylic acids) and have computed the contributions of the three-carbon ring from the relationship given above ($n = 1$). The necessary experimental data were taken from earlier papers of this series (2H from Part IX, alkyl *n*-butyrates and alkyl ethylmalonates from Part XIII, this vol., p. 624; the data for *n*-butyric acid are given in Part XX, *ibid.*, p. 1814). The results are summarised in Table I; the experimental data for dimethyl *cyclo*propane-1 : 1-dicarboxylate were taken from Part I (*J.*, 1934, 340). The slight (and often negative) difference between R_F and $R_{G'}$ is noteworthy; it is hoped to repeat

TABLE I.

Values for the three-carbon ring from cyclo*propane compounds.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	Mn_D^{20}.
*cyclo*Propanecarboxylic acid.....	14·0	0·59	0·61	0·65	0·66	−4·44
*cyclo*Propyl methyl ketone	13·3	0·69	0·72	0·78	0·78	−5·00
Me *cyclo*propanecarboxylate.....	13·4	0·59	0·61	0·65	0·64	−4·78
Et *cyclo*propanecarboxylate	12·6	0·54	0·60	0·60	0·60	−4·67
Pr^n *cyclo*propanecarboxylate.....	12·4	0·61	0·62	0·66	0·66	−4·59
Bu^n *cyclo*propanecarboxylate	12·0	0·61	0·63	0·67	0·66	−4·81
Am^n *cyclo*propanecarboxylate	11·3	0·49	0·52	0·56	0·55	−4·85
Me_2 *cyclo*propane-1 : 1-dicarboxylate	12·3	0·63	0·63	0·68	0·65	−4·46
Et_2 *cyclo*propane-1 : 1-dicarboxylate	11·2	0·58	0·59	0·65	0·61	−4·91
$Pr^n{}_2$ *cyclo*propane-1 : 1-dicarboxylate	10·5	0·45 *	0·44 *	0·51 *	0·48 *	−4·73
Mean (excluding *) ▷	12·3	0·592	0·614	0·656	0·646	−4·72
Mean ▷	12·3	0·578	0·597	0·641	0·629	−4·73

the measurements for n_F and $n_{G'}$ with the new Hilger–Chance refractometer to establish whether the differences are due to experimental error in the measurement of the faint G′ line or whether these are characteristic of *cyclo*propane compounds. It will be noted that two values of the mean

constants are given in the table; the first set of figures, which excludes the apparently low results for di-*n*-propyl *cyclo*propane-1 : 1-dicarboxylate, is considered to be more trustworthy.

The contributions of the four-membered carbon ring have been similarly calculated from new measurements upon esters of *cyclo*butane-carboxylic and -1 : 1-dicarboxylic acids and upon the first acid itself; the reference data for alkyl *n*-valerates and *n*-propylmalonates are given in Part XIII and for *n*-valeric acid in Part XX (*locc. cit.*). Precision measurements with the Hilger–Chance refractometer must decide whether the apparently anomalous values for $R_{G'}$ are real or are due to experimental error. The results are collected in Table II.

TABLE II.

Values for the four-carbon ring from cyclo*butane compounds.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
*cyclo*Butanecarboxylic acid	11·1	0·36	0·37	0·38	0·37	−4·40
Me *cyclo*butanecarboxylate	10·0	0·31	0·33	0·33	0·32	−4·63
Et *cyclo*butanecarboxylate	10·2	0·29	0·31	0·32	0·32	−4·68
Pr^n *cyclo*butanecarboxylate	10·0	0·32	0·35	0·34	0·35	−4·78
Bu^n *cyclo*butanecarboxylate	10·3	0·36	0·36	0·38	0·38	−4·72
Am^n *cyclo*butanecarboxylate	9·9	0·26	0·29	0·29	0·28	−4·63
Me_2 *cyclo*butane-1 : 1-dicarboxylate	10·2	0·32	0·34	0·37	0·34	−4·48
Et_2 *cyclo*butane-1 : 1-dicarboxylate	9·5	0·26	0·26	0·29	0·28	−4·83
Pr^n_2 *cyclo*butane-1 : 1-dicarboxylate	9·7	0·31	0·31	0·35	0·34	−4·82
Bu^n_2 *cyclo*butane-1 : 1-dicarboxylate	9·2	0·24	0·25	0·27	0·24	−4·71
Mean ◇	10·0	0·303	0·317	0·332	0·322	−4·67

EXPERIMENTAL.

Physical Measurements.—Full details applying to this and the subsequent papers of this series are given in Part VII (*J.*, 1943, 18). Surface tensions were measured by the method of capillary rise, and only the values for H ($= h - 0·24$ mm.) are given. The constants for the various apparatus are: *A* 1·8725, *B* 2·3449, *C* 2·3740, *D* 2·4696, *E* 2·3290, *F* 2·3282. Unless otherwise stated, all b. p.s are corrected. Measurements of the refractive indices were made at 20° ± 0·05° on a Zeiss Pulfrich refractometer; with some compounds the G′ line was so faint that setting of the crosswires was less accurate than for the *C* and *F* lines.

Previous Work.—The larger proportion of the measurements described in this and succeeding papers of this series are new. The constants deduced will in all cases be based upon the measurements from this laboratory. In order to economise space, no reference will be made (save in exceptional circumstances) to previous work since this can be found in I.C.T., Landolt–Börnstein "Tabellen", or the original literature.

Preparation of Pure Compounds.—cyclo*Propyl methyl ketone.* The Eastman–Kodak product was dried ($CaSO_4$) and distilled through a Widmer column in an all-glass apparatus. A middle fraction, b. p. 111°/757 mm. (semicarbazone, m. p. 117°), was used for the physical measurements.

cyclo*Propanecarboxylic acid.* Decomposition of *cyclo*propane-1 : 1-dicarboxylic acid, m. p. 136—137°, by heating at 160° until evolution of carbon dioxide ceased yielded crude *cyclo*propanecarboxylic acid, b. p. 185—195°. The physical properties of the liquid were anomalous owing to the presence of a considerable quantity of γ-butyrolactone (Perkin, *J.*, 1885, **47**, 815; Bone and Perkin, *J.*, 1895, **67**, 117); a middle fraction, b. p. 188°, had $d_{4°}^{20°}$ 1·1148, $n_D^{20°}$ 1·4395. Upon dissolving the crude acid in dilute sodium carbonate solution, extracting with ether to remove the butyrolactone, acidifying with dilute sulphuric acid at 0°, and extracting with ether, fairly pure *cyclo*propanecarboxylic acid, b. p. 184—185°, was obtained in poor yield: this had $d_{4°}^{20°}$ 1·0891, $n_D^{20°}$ 1·4376 (Bruylants, *Bull. Soc. chim. Belg.*, 1929, **38**, 133, gives $d_{4°}^{20°}$ 1·0885, $n_D^{20°}$ 1·43901 for the acid presumably prepared by hydrolysis of *cyclo*propyl cyanide).

The most convenient method for the preparation of the pure acid in quantity was the oxidation of the readily available *cyclo*propyl methyl ketone (compare *Org. Synth.*, 1944, **24**, 36). In a 3-l. three-necked flask, equipped with a dropping funnel, mechanical stirrer, and thermometer, was placed a solution of 165 g. of sodium hydroxide in 1400 ml. of water, cooled to 0—2°, and 240 g. of A.R. bromine were added with stirring at such a rate that the temperature did not rise above 10°. The sodium hypobromite solution was cooled to 0°; redistilled *cyclo*propyl methyl ketone, b. p. 110·5—111·5°/757 mm., was added with stirring so that the temperature did not rise above 10°. The ice-bath was then removed, and the stirring continued for a further 2 hours. The mixture was steam-distilled to remove the bromoform (105—115 g.; a little solid carbon tetrabromide may separate in the condenser). The liquid was cooled in ice, acidified to Congo-red with concentrated hydrochloric acid, a little sodium hydrogen sulphite added to remove the very pale yellow colour, and the acid isolated by saturation with salt and extraction with ether (4 × 300 ml.). Removal of the solvent and distillation under reduced pressure yielded 36 g. of pure *cyclo*propanecarboxylic acid, b. p. 97°/27 mm., m. p. 17—17·5°. Slight decomposition occurs upon distillation at atmospheric pressure: b. p. 179—180°, m. p. 15·5—16·5°.

Methyl cyclo*propanecarboxylate.* An all-glass apparatus, provided with a reflux condenser and dropping funnel, was charged with 100 g. of redistilled thionyl chloride and 52 g. of pure *cyclo*propanecarboxylic acid were slowly added. The mixture was refluxed for 30 minutes and then distilled through an all-glass Dufton column; 53 g. of the acid chloride, b. p. 119—119·5°/763 mm., were collected.

10·5 G. of pure anhydrous methyl alcohol were placed in an all-glass apparatus (50 ml. round-bottomed flask fitted with an adapter carrying a condenser and a dropping funnel equipped with guard tubes), cooled in ice, and 33 g. of the acid chloride added during 30 minutes. The mixture was kept at room

temperature for 5 hours, poured into water, the ester separated, washed successively with saturated sodium hydrogen carbonate solution and water, dried ($CaSO_4$), and distilled. The yield of ester, b. p. 117·5°/761 mm., was 11 g.

Ethyl cyclo*propanecarboxylate*. 10·1 G. of absolute ethyl alcohol and 22 g. of the acid chloride, after standing at room temperature for 90 minutes, gave 13 g. of the ester, b. p. 133°/763 mm.

n-*Propyl* cyclo*propanecarboxylate*. 13·2 G. of absolute *n*-propyl alcohol and 22 g. of the acid chloride, after standing at room temperature for 5 hours, afforded 13 g. of the *ester*, b. p. 155°/766 mm. (Found: C, 65·8; H, 9·2. $C_7H_{12}O_2$ requires C, 65·6; H, 9·4%).

n-*Butyl* cyclo*propanecarboxylate*. 11·8 G. of pure *n*-butyl alcohol and 16 g. of the acid chloride gave, after standing for 1 hour at room temperature, 19 g. of the *ester*, b. p. 175°/759 mm. (Found: C, 67·5; H, 9·7. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%).

n-*Amyl* cyclo*propanecarboxylate*. 13·2 G. of Boots synthetic *n*-amyl alcohol and 15 g. of the acid chloride gave, after standing for 1 hour at room temperature, 13 g. of the ester, b. p. 193°/753 mm. Redistillation yielded the pure *ester*, b. p. 87°/17 mm. (Found: C, 69·1; H, 10·1. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%).

cyclo*Propane*-1 : 1-*dicarboxylic acid*. This was prepared by condensation of ethyl sodiomalonate [from sodium, " super-dry " ethyl alcohol (by ethyl phthalate method), and dry ethyl malonate] and dry ethylene dibromide (compare Part I, *J.*, 1934, 337) or preferably from ethyl sodiocyanoacetate and ethylene dibromide (compare Carpenter and Perkin, *J.*, 1899, **75**, 924; Jones and Scott, *J. Amer. Chem. Soc.*, 1922, **44**, 413). The acid is best isolated by continuous ether extraction, and after two recrystallisations from ether–light petroleum (b. p. 60—80°) had m. p. 136—137°.

Diethyl cyclo*propane*-1 : 1-*dicarboxylate*. A mixture of 19·5 g. of the acid, 28 g. of absolute ethyl alcohol, 9 g. of concentrated sulphuric acid, and 55 ml. of sodium-dried A.R. benzene was refluxed for 20 hours and then poured into excess of water. The benzene layer was separated, the aqueous phase was extracted once with ether, and the combined benzene and ether extracts washed successively with water, saturated sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), the solvents removed at atmospheric pressure, and the residue distilled under reduced pressure. The yield of diethyl ester, b. p. 114°/22 mm., was 16 g.

Di-n-*propyl* cyclo*propane*-1 : 1-*dicarboxylate*. A similar preparation, but with 42 g. of absolute *n*-propyl alcohol, gave 17 g. of *di*-n-*propyl* cyclo*propane*-1 : 1-*dicarboxylate*, b. p. 124°/12 mm. (Found: C, 61·5; H, 8·7. $C_{11}H_{18}O_4$ requires C, 61·7; H, 8·5%).

cyclo*Butane*-1 : 1-*dicarboxylic acid*. The yield of acid obtained by condensation of 212 g. of trimethylene dibromide with ethyl sodiomalonate (from 46 g. of sodium, 800 ml. of absolute ethyl alcohol, and 160 g. of ethyl malonate) according to the procedure of *Org. Synth.*, 1943, **23**, 16 (compare Perkin, *J.*, 1887, **51**, 1) can be increased from 30—34 g. to 50—51 g. by the use of perfectly dry materials, *i.e.*, trimethylene dibromide and ethyl malonate dried over anhydrous calcium sulphate, and absolute ethyl alcohol dried by the ethyl phthalate method. The resulting *cyclo*butane-1 : 1-dicarboxylic acid has m. p. 158° unaffected by recrystallisation.

Dimethyl cyclo*butane*-1 : 1-*dicarboxylate*. A mixture of 21·6 g. of the acid, 20 g. of absolute methyl alcohol, 9 g. of concentrated sulphuric acid, and 50 ml. of sodium-dried A.R. benzene was refluxed for 22 hours and yielded, when worked up as detailed for diethyl *cyclo*propane-1 : 1-dicarboxylate, 17 g. of ester, b. p. 87°/8 mm.

Diethyl cyclo*butane*-1 : 1-*dicarboxylate*. This ester was similarly prepared from 28 g. of absolute ethyl alcohol; yield 16 g., b. p. 101·5°/11 mm.

Di-n-*propyl* cyclo*butane*-1 : 1-*dicarboxylate*. In like manner, but from 42 g. of absolute *n*-propyl alcohol and with 34 hours' refluxing, 23 g. of this *ester*, b. p. 129°/13 mm. (Found: C, 63·3; H, 8·8. $C_{12}H_{20}O_4$ requires C, 63·1; H, 8·8%), were obtained.

Di-n-*butyl* cyclo*butane*-1 : 1-*dicarboxylate*. A mixture of 14·4 g. of the acid, 28·2 g. of pure *n*-butyl alcohol, 6 g, of concentrated sulphuric acid, and 40 ml. of dry benzene was refluxed for 22 hours and gave 16 g. of the *ester*, b. p. 146°/11 mm. (Found: C, 65·7; H, 9·3. $C_{14}H_{24}O_4$ requires C, 65·6; H, 9·4%).

cyclo*Butanecarboxylic acid*. The 1 : 1-dicarboxylic acid, m. p. 158°, was decomposed by heating above the m. p. (*Org. Synth.*, 1943, **23**, 17) and gave an 88% yield of the pure acid, b. p. 195·5°/765 mm. (compare *op. cit.*, which gives b. p. 191·5—193·5°/740 mm.).

Methyl cyclo*butanecarboxylate*. The reaction between 100 g. of redistilled thionyl chloride and 65 g. of pure *cyclo*butanecarboxylic acid yielded, as for the *cyclo*propane compound, 62 g. of the acid chloride, b. p. 136—137°/762 mm.

The preparation of all the esters from this acid chloride was conducted as detailed for methyl *cyclo*propanecarboxylate; after the addition of the acid chloride to the appropriate alcohol cooled to 0°, the mixture was kept at room temperature for 60—90 minutes before being poured into water, etc. Thus 38 g. of the acid chloride and 15 g. of absolute methyl alcohol afforded 30 g. of methyl *cyclo*butanec arboxylate, b. p. 134·5°/764 mm.

Ethyl cyclo*butanecarboxylate*. From 18 g. of the acid chloride and 8·0 g. of absolute ethyl alcohol, the yield of ester, b. p. 152°/762 mm., was 13 g.

n-*Propyl* cyclo*butanecarboxylate*. From 22·5 g. of the acid chloride and 13·0 g. of pure *n*-propyl alcohol, the yield of *ester*, b. p. 172°/765 mm., was 23 g. (Found: C, 67·5; H, 9·9. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%).

n-*Butyl* cyclo*butanecarboxylate*. From 20·1 g. of acid chloride and 13·8 g. of absolute *n*-butyl alcohol, the yield of *ester*, b. p. 98°/32 mm., was 22 g. (Found: C, 69·2; H, 10·2. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%).

n-*Amyl* cyclo*butanecarboxylate*. From 22·0 g. of the acid chloride and 19·4 g. of Boots synthetic *n*-amyl alcohol, the yield of *ester*, b. p. 105°/20 mm., was 22 g. (Found: C, 70·5; H, 10·8. $C_{10}H_{18}O_2$ requires C, 70·6; H, 10·7%).

The results of the physical measurements upon the freshly distilled compounds are collected below. The numbering of compounds in Clarendon type follows from Part XVII (this vol., p. 683). Reference to

compounds, the preparation of which is described in preceding or succeeding papers of this series, will be abbreviated to, *e.g.*, XVII, **418**.

419. cyclo*Propyl methyl ketone.* B. p. 111°/757 mm.; *M* 84·11; n_C 1·42243, n_D 1·42496, n_F 1·43116, $n_{G'}$ 1·43555; R_C 23·78, R_D 23·91, R_F 24·22, $R_{G'}$ 24·43; $Mn_D^{20°}$ 119·86. Densities determined: $d_{4°}^{20°}$ 0·8994, $d_{4°}^{40·0°}$ 0·8803, $d_{4°}^{63·7°}$ 0·8575, $d_{4°}^{87·7°}$ 0·8332. Apparatus *E*.

(These headings apply to all subsequent tables in this paper.)

t.	*H.*	$d^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
17·9°	14·67	0·9014	30·80	219·8	60·9°	12·77	0·8602	25·58	219·9
21·3	14·54	0·8981	30·41	219·9	87·1	11·67	0·8338	22·66	220·1
40·9	13·67	0·8794	28·00	220·0				Mean	219·9

420. cyclo*Propanecarboxylic acid.* B. p. 97°/27 mm., m. p. 17·5°; *M* 86·09; n_C 1·43562, n_D 1·43832, n_F 1·44448, $n_{G'}$ 1·44922; R_C 20·65, R_D 20·77, R_F 21·02, $R_{G'}$ 21·21; $Mn_D^{20°}$ 123·82. Densities determined: $d_{4°}^{20°}$ 1·0889, $d_{4°}^{40·0°}$ 1·0707, $d_{4°}^{60·2°}$ 1·0514, $d_{4°}^{86·5°}$ 1·0262. Apparatus *E*.

22·4°	13·55	1·0867	34·29	191·7	60·9°	12·31	1·0508	30·13	191·9
40·1	12·95	1·0706	32·29	191·7	85·9	11·56	1·0267	27·64	192·3
								Mean	191·9

421. *Methyl* cyclo*propanecarboxylate.* B. p. 117·5°/763 mm.; *M* 100·11; n_C 1·41637, n_D 1·41866, n_F 1·42424, $n_{G'}$ 1·42825; R_C 25·21, R_D 25·34, R_F 25·63, $R_{G'}$ 25·84; $Mn_D^{20°}$ 142·03. Densities determined: $d_{4°}^{20°}$ 0·9972, $d_{4°}^{40·3°}$ 0·9759, $d_{4°}^{63·6°}$ 0·9508, $d_{4°}^{86·5°}$ 0·9272. Apparatus *E*.

20·0°	13·26	0·9972	30·80	236·5	61·5°	11·54	0·9530	25·61	236·3
23·1	13·18	0·9940	30·51	236·7	86·2	10·52	0·9275	22·72	236·0
40·9	12·37	0·9753	28·10	236·3				Mean	236·4

422. *Ethyl* cyclo*propanecarboxylate.* B. p. 133°/763 mm.; *M* 114·14; n_C 1·41789, n_D 1·42076, n_F 1·42573, $n_{G'}$ 1·42979; R_C 29·84, R_D 30·02, R_F 30·33, $R_{G'}$ 30·58; $Mn_D^{20°}$ 162·17. Densities determined: $d_{4°}^{20°}$ 0·9638, $d_{4°}^{40·0°}$ 0·9434, $d_{4°}^{63·4°}$ 0·9196, $d_{4°}^{86·2°}$ 0·8949. Apparatus *E*.

20·9°	12·94	0·9629	29·02	275·1	61·1°	11·28	0·9219	24·22	274·7
41·3	12·15	0·9421	26·66	275·3	85·9	10·36	0·8952	21·60	274·9
								Mean	275·0

423. n-*Propyl* cyclo*propanecarboxylate.* B. p. 155°/766 mm.; *M* 128·27; n_C 1·42216, n_D 1·42446, n_F 1·43011, $n_{G'}$ 1·43395; R_C 34·54, R_D 34·70, R_F 35·10, $R_{G'}$ 35·38; $Mn_D^{20°}$ 182·72. Densities determined: $d_{4°}^{20°}$ 0·9441, $d_{4°}^{41·0°}$ 0·9240, $d_{4°}^{62·8°}$ 0·9029, $d_{4°}^{87·3°}$ 0·8794. Apparatus *E*.

19·8°	13·21	0·9443	29·05	315·4	61·2°	11·58	0·9044	24·39	315·2
22·7	13·08	0·9415	28·68	315·2	85·7	10·68	0·8809	21·91	315·0
40·7	12·34	0·9243	26·56	315·1				Mean	315·2

424. n-*Butyl* cyclo*propanecarboxylate.* B. p. 175°/759 mm.; *M* 142·19; n_C 1·42620, n_D 1·42847, n_F 1·43404, $n_{G'}$ 1·43813; R_C 39·17, R_D 39·36, R_F 39·80, $R_{G'}$ 40·12; $Mn_D^{20°}$ 203·12. Densities determined: $d_{4°}^{20°}$ 0·9304, $d_{4°}^{40·0°}$ 0·9136, $d_{4°}^{61·5°}$ 0·8944, $d_{4°}^{85·6°}$ 0·8714. Apparatus *E*.

25·8°	13·16	0·9254	28·36	354·6	62·2°	11·82	0·8936	24·60	354·4
40·7	12·58	0·9130	26·75	354·2	85·7	10·96	0·8713	22·24	354·4
								Mean	354·4

425. n-*Amyl* cyclo*propanecarboxylate.* B. p. 193°/753 mm. followed by 87°/17 mm.; *M* 156·22; n_C 1·42976, n_F 1·43219, n_F 1·43765, $n_{G'}$ 1·44174; R_C 43·74, R_D 43·96, R_F 44·45, $R_{G'}$ 44·80; $Mn_D^{20°}$ 223·74. Densities determined: $d_{4°}^{20°}$ 0·9221, $d_{4°}^{41·5°}$ 0·9034, $d_{4°}^{60·4°}$ 0·8870, $d_{4°}^{85·9°}$ 0·8639. Apparatus *E*.

15·6°	13·73	0·9259	29·61	393·6	61·5°	11·99	0·8861	24·74	393·2
40·5	12·84	0·9043	27·04	393·9	86·7	11·14	0·8623	22·37	394·0
								Mean	393·7

426. *Diethyl* cyclo*propane*-1 : 1-*dicarboxylate.* B. p. 114°/22 mm.; *M* 186·20; n_C 1·43078, n_D 1·43310, n_F 1·43881, $n_{G'}$ 1·44264; R_C 45·38, R_D 45·60, R_F 46·12, $R_{G'}$ 46·47; $Mn_D^{20°}$ 266·84. Densities determined: $d_{4°}^{20°}$ 1·0615, $d_{4°}^{40·0°}$ 1·0419, $d_{4°}^{60·5°}$ 1·0217, $d_{4°}^{85·3°}$ 0·9962. Apparatus *E*.

16·2°	12·99	1·0653	32·23	416·5	60·3°	11·50	1·0219	27·37	416·8
19·9	12·88	1·0616	31·85	416·7	86·2	10·71	0·9953	24·83	417·6
41·3	12·10	1·0406	29·33	416·4				Mean	416·8

427. *Di*-n-*propyl* cyclo*propane*-1 : 1-*dicarboxylate.* p. 124°/12 mm.; *M* 214·25; n_C 1·43520, n_D 1·43751, n_F 1·44321, $n_{G'}$ 1·44711; R_C 54·57, R_D 54·82, R_F 55·44, $R_{G'}$ 55·87; $Mn_D^{20°}$ 307·98. Densities determined: $d_{4°}^{20°}$ 1·0249, $d_{4°}^{40·5°}$ 1·0052, $d_{4°}^{60·6°}$ 0·9864, $d_{4°}^{86·7°}$ 0·9622. Apparatus *E*.

18·7°	13·16	1·0262	31·45	494·4	61·5°	11·64	0·9854	26·71	494·3
40·4	12·28	1·0053	28·75	493·5	86·8	10·85	0·9621	24·31	494·5
								Mean	494·2

428. *Dimethyl* cyclo*butane*-1 : 1-*dicarboxylate.** B. p. 87°/8 mm.; M 172·18; n_C 1·43920, n_D 1·44154, n_F 1·44079, $n_{G'}$ 1·45100; R_C 40·52, R_D 40·70, R_F 41·15, $R_{G'}$ 41·46; $Mn_D^{20°}$ 248·20. Densities determined: $d_4^{20°}$ 1·1182, $d_4^{40·2°}$ 1·0981, $d_4^{60·3°}$ 1·0786, $d_4^{91·9°}$ 1·0464. Apparatus E.

t.	H.	$d_{4°}^{t°}$.	γ.	P.	t.	H.	$d_{4°}^{t°}$.	γ.	P.
20·4°	13·49	1·1178	35·12	375·0	60·8°	12·12	1·0781	30·43	375·1
40·1	12·76	1·09882	32·62	374·7	85·0	11·30	1·0532	27·72	375·1
								Mean	375·0

429. *Diethyl* cyclo*butane*-1 : 1-*dicarboxylate*. B. p. 101·5°/11 mm.; M 200·23; n_C 1·43364, n_D 1·43590, n_F 1·44140, $n_{G'}$ 1·44539; R_C 49·78, R_D 50·01, R_F 50·56, $R_{G'}$ 50·96; $Mn_D^{20°}$ 287·51. Densities determined: $d_4^{20°}$ 1·0466, $d_4^{40·2°}$ 1·0271, $d_4^{60·8°}$ 1·0075, $d_4^{86·0°}$ 0·9831. Apparatus *E*.

13·4°	13·14	1·0530	32·22	453·1	60·1°	11·59	1·0082	27·21	453·6
18·9	12·98	1·0477	31·67	453·4	87·1	10·72	0·9820	24·52	453·7
40·2	12·33	1·0271	29·49	454·3				Mean	453·6

430. *Di*-n-*propyl* cyclo*butane*-1 : 1-*dicarboxylate*. B. p. 129°/13 mm.; M 228·28; n_C 1·43689, n_D 1·43913, n_F 1·44467, $n_{G'}$ 1·44875; R_C 59·07, R_D 59·33, R_F 59·99, $R_{G'}$ 60·47; $Mn_D^{20°}$ 328·52. Densities determined: $d_4^{20°}$ 1·0122, $d_4^{40·9°}$ 0·9937, $d_4^{60·0°}$ 0·9767, $d_4^{86·7°}$ 0·9527. Apparatus *E*.

25·1°	12·89	1·0077	30·22	531·3	61·3°	11·73	0·9755	26·65	531·7
40·4	12·38	0·9941	28·66	531·3	86·4	10·95	0·9530	24·30	531·9
								Mean	531·6

431. *Di*-n-*butyl* cyclo*butane*-1 : 1-*dicarboxylate*. B. p. 146°/11 mm.; M 256·33; n_C 1·43976, n_D 1·44205, n_F 1·44765, $n_{G'}$ 1·45163; R_C 68·18, R_D 68·49, R_F 69·24, $R_{G'}$ 69·76; $Mn_D^{20°}$ 369·65. Densities determined: $d_4^{20°}$ 0·9905, $d_4^{40·6°}$ 0·9724, $d_4^{59·7°}$ 0·9566, $d_4^{85·9°}$ 0·9905. Apparatus *E*.

23·9°	13·03	0·9871	29·96	607·5	61·1°	11·83	0·9544	26·20	608·3
40·7	12·57	0·9723	28·46	608·9	86·2	11·15	0·9344	24·26	609·1
								Mean	608·5

432. cyclo*Butanecarboxylic acid*. B. p. 195·5°/772 mm.; M 100·11; n_C 1·44115, n_D 1·44355, n_F 1·44932, $n_{G'}$ 1·45337; R_C 25·02, R_D 25·14, R_F 25·42, $R_{G'}$ 25·62; $Mn_D^{20°}$ 144·52. Densities determined: $d_4^{20°}$ 1·0570, $d_4^{40·0°}$ 1·0399, $d_4^{60·5°}$ 1·0217. $d_4^{85·3°}$ 0·9997. Apparatus *A*.

22·8°	16·93	1·0546	33·43	228·3	60·2°	15·47	1·0220	29·60	228·5
28·5	16·66	1·0496	32·74	228·2	86·9	14·34	0·9983	26·81	228·2
40·3	16·12	1·0396	31·38	227·8				Mean	228·2

433. *Methyl* cyclo*butanecarboxylate*. B. p. 134·5°/754 mm.; M 114·14; n_C 1·42354, n_D 1·42596, n_F 1·43111, $n_{G'}$ 1·43505; R_C 29·56, R_D 29·71, R_F 30·02, $R_{G'}$ 30·26; $Mn_D^{20°}$ 162·76. Densities determined: $d_4^{20°}$ 0·9844, $d_4^{39·8°}$ 0·9645, $d_4^{61·5}$ 0·9429, $d_4^{86·9°}$ 0·9161. Apparatus *E*.

19·3°	13·54	0·9851	31·06	273·6	61·9°	11·74	0·9425	25·77	272·9
42·3	12·43	0·9620	27·85	272·6	86·8	10·76	0·9162	22·96	272·7
								Mean	273·0

434. *Ethyl* cyclo*butanecarboxylate*. B. p. 152°/762 mm.; M 128·17; n_C 1·42353, n_D 1·42581, n_F 1·43103, $n_{G'}$ 1·43498; R_C 34·24, R_D 34·41, R_F 34·78, $R_{G'}$ 35·06; $Mn_D^{20°}$ 192·74. Densities determined: $d_4^{20°}$ 0·9540, $d_4^{40·2°}$ 0·9346, $d_4^{60·7°}$ 0·9143, $d_4^{86·3°}$ 0·8895. Apparatus *E*.

15·1°	13·46	0·9589	30·06	313·0	61·7°	11·52	0·9133	24·50	312·2
20·9	13·22	0·9531	29·35	313·0	89·1	10·45	0·8863	21·57	311·7
40·7	12·30	0·9341	26·76	312·1				Mean	312·4

435. n-*Propyl* cyclo*butanecarboxylate*. B. p. 172°/765 mm.; M 142·19; n_C 1·42680, n_D 1·42912, n_F 1·43430, $n_{G'}$ 1·43835; R_C 38·86, R_D 39·06, R_F 39·46, $R_{G'}$ 39·79; $Mn_D^{20°}$ 203·20. Densities determined: $d_4^{20°}$ 0·9389, $d_4^{42·5°}$ 0·9181, $d_4^{61·3°}$ 0·9007, $d_4^{86·8°}$ 0·8766. Apparatus *E*.

17·2°	13·43	0·9415	29·45	351·8	63·2°	11·74	0·8980	24·55	352·5
41·4	12·59	0·9191	26·95	352·5	87·6	10·85	0·8758	22·13	352·1
								Mean	352·2

436. n-*Butyl* cyclo*butanecarboxylate*. B. p. 98°/32 mm.; M 156·22; n_C 1·43052, n_D 1·43274, n_F 1·43809, $n_{G'}$ 1·44200; R_C 43·46, R_D 43·66, R_F 44·13, $R_{G'}$ 44·48; $Mn_D^{20°}$ 223·82. Desnities determined: $d_4^{20°}$ 0·9294, $d_4^{42·7°}$ 0·9093, $d_4^{62·8°}$ 0·8924, $d_4^{88·2°}$ 0·8732. Apparatus *E*.

15·4°	13·74	0·9334	29·87	391·3	61·9°	12·10	0·8928	25·16	391·9
18·3	13·61	0·9309	29·51	391·1	86·3	11·30	0·8722	22·95	392·0
41·6	12·82	0·9101	27·17	391·9				Mean	391·6

* The results for this new preparation supersede those in Part I, *J.*, 1934, 340.

437. n-*Amyl* cyclo*butanecarboxylate*. B. p. 105°/20 mm.; *M* 170·24; n_C 1·43362, n_D 1·43600, n_F 1·44131, $n_{G'}$ 1·44533; R_C 48·06, R_D 48·30, R_F 48·80, $R_{G'}$ 49·19; $Mn_D^{20°}$ 244·46. Densities determined: $d_{4°}^{20°}$ 0·9217, $d_{4°}^{41·6°}$ 0·9031, $d_{4°}^{61·3°}$ 0·8863, $d_{4°}^{85·7°}$ 0·8652. Apparatus *E*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
16·1°	13·85	0·9251	29·84	430·1	61·7°	12·24	0·8860	25·26	430·7
41·3	12·91	0·9034	27·16	430·2	86·8	11·43	0·8643	23·01	431·4
								Mean	430·6

The authors' thanks are due to Sharples Chemicals Inc., of Philadelphia, U.S.A., for a gift of *cyclo*propyl methyl ketone.

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365. *Physical Properties and Chemical Constitution. Part XIX. Five-membered and Six-membered Carbon Rings.*

By ARTHUR I. VOGEL.

New experimental data are provided for the calculation of the refractivities at 20° and the parachors of a number of *cyclo*pentane and *cyclo*hexane derivatives. These and those described in Part III (*J.*, 1938, 1338) have been employed in the computation of the constants for the 5-membered and 6-membered carbon rings respectively. The mean values, excluding ketones and halides, are as follows:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
5-Membered carbon ring	4·6	−0·19	−0·19	−0·19	−0·22	−4·56
6-Membered carbon ring	1·4	−0·15	−0·15	−0·16	−0·17	−3·53

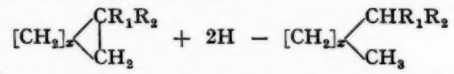
THE view seems generally accepted (see, *e.g.*, Eisenlohr, "Spektrochemie organischer Verbindungen: Molekularrefraktion und -dispersion", Ferdinand Enke, 1912, 86) that the contributions of the 5- and 6-membered carbon rings to the molecular refraction are zero. Ruzicka and Boekenoogen (*Helv. Chim. Acta*, 1931, **14**, 1323; compare Ruzicka *et al.*, *ibid.*, 1930, **13**, 1158) find the ring increments for 5-, 7-, 8-, and 15-rings to be + 0·04, − 0·10, − 0·47, and − 0·62 respectively, that for the 6-ring being assumed to be zero. They use Eisenlohr's value for CH_2 for the D line of 4·62; the correct value is, however, 4·647 (Part IX, *J.*, 1946, **133**). Sugden (*J.*, 1924, **125**, 1180) assigns values of 8·5 and 6·1 (compare Sugden and Wilkins, *J.*, 1927, 142) to the 5- and 6-membered rings respectively; the data from which these constants were calculated were not stated, but a value for CH_2 of 39·0 was employed. A comparison of the physical properties of the following isomeric compounds suggests that the contributions of

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Methyl*cyclo*pentane (I)	243·8	27·63	27·77	28·07	28·24	118·67
Methyl*cyclo*pentane (II)	—	27·79	27·90	28·12	28·46	118·54
Methyl*cyclo*pentane (III)	243·9	27·69	27·82	28·12	28·36	118·57
*cyclo*Hexane.....	241·8	27·63	27·75	28·05	28·27	120·06
Methyl*cyclo*hexane.....	280·9	32·36	32·53	32·87	33·12	139·82
*cyclo*Heptane	278·9	32·01	32·18	32·53	32·76	141·73
1-Methyl-Δ^2-*cyclo*pentene	232·9	27·10	27·25	27·51	27·86	117·03
*cyclo*Hexene.....	230·4	29·96	27·11	27·47	27·74	118·82
1-Methyl-Δ^1-*cyclo*hexene	269·4	31·66	31·84	32·26	32·57	139·51
*cyclo*Heptene	268·2	31·58	31·75	32·17	32·49	140·16
3-Methyl*cyclo*pentanol	255·0	29·22	29·37	29·66	29·89	144·97
*cyclo*Hexanol (supercooled)	253·3	29·04	29·16	29·48	29·71	146·83

the rings to the molecular refractivity, although small, are not zero. The data are extracted from Part III (*J.*, 1938, 1323); under methyl*cyclo*pentane, I was prepared from 3-methyl*cyclo*pentanone, II from 1-methyl*cyclo*pentan-1-ol (Eisenlohr, "Fortschritte der Chemie, Physik und physikalischen Chemie", 1925, Band 18, Heft 9, p. 23), and III by heating *cyclo*hexane with aluminium chloride (Wibaut *et al.*, *Rec. Trav. chim.*, 1939, **58**, 365). The results for the methylene hydrocarbons (Part III, *loc. cit.*) have been omitted since the compounds were by-products in thermal decomposition reactions and consequently their absolute purity is doubtful.

The problem was systematically investigated with the aid of the experimental data given in

Part III (*loc. cit.*) and the new results are recorded in the experimental section. The ring contributions were computed from the relationship :



The constants for 2H were taken from Part IX (*loc. cit.*), and those for the other reference compounds from earlier papers of this series : for *cyclo*pentane the constants are obtained directly by subtracting $5 \times CH_2$. All the results for the *cyclo*pentane ring are collected in Table I.

TABLE I.

Values for the five-carbon ring from cyclo*pentane compounds.*

	P.	R_C.	R_D.	R_F.	$R_{C'}$.	$Mn_D^{20°}$.
*cyclo*Pentane	4·9	−0·15	−0·15	−0·14	−0·17	−4·30
Methyl*cyclo*pentane	4·3	−0·11	−0·10	−0·09	−0·15	−4·94
*cyclo*Pentene	4·5	−0·38	−0·37	−0·39	−0·43	−4·89
1-Methyl-Δ^2-*cyclo*pentene	3·7	−0·13	−0·13	−0·14	−0·14	−5·22
*cyclo*Pentanol	5·0	−0·21	−0·21	−0·22	−0·22	−4·25
*cyclo*Pentyl methyl ether	4·0	−0·16	−0·17	−0·18	−0·21	−4·59
*cyclo*Pentyl ethyl ether	4·1	−0·20	−0·19	−0·19	−0·23	−4·53
*cyclo*Pentyl formate	5·2	−0·22	−0·22	−0·22	−0·25	−4·25
*cyclo*Pentyl acetate	5·9	−0·13	−0·14	−0·14	−0·16	−4·16
Mean	4·6	−0·19	−0·19	−0·19	−0·22	−4·56
*cyclo*Pentanone	7·5	0·11	0·12	0·12	0·10	−4·01
3-Methyl*cyclo*pentanone	5·7	0·10	0·07	0·11	—	−4·73
*cyclo*Pentyl chloride	5·2	−0·06	−0·04	−0·02	−0·03	−3·85
*cyclo*Pentyl bromide	6·3	0·07	0·06	0·08	0·05	−1·56
*cyclo*Pentyl iodide	7·9	0·19	0·21	0·24	0·23	1·99

In the calculation of the mean values, the results for the cyclic ketones and cyclic halides have been omitted. No definite explanation can be offered of the apparently anomalous refractivities of these compounds; whether these are in fact real and are characteristic of the compounds or whether the differences are due to experimental error is an open question. The latter explanation is the more probable, since the preparation of perfectly pure cyclic halides is extremely difficult; this would suggest that ketones prepared by the decomposition of the pure semicarbazones with aqueous oxalic acid are not as pure as is generally supposed.

The results for the *cyclo*hexane compounds are summarised in Table II : the constants for the ketones and halides are not included in the calculation of the mean values; the two sets of figures for 3-methyl*cyclo*hexanone were obtained by the use of the two alternative reference compounds, methyl *n*-amyl ketone and di-*n*-propyl ketone, respectively (Part V, *J.*, 1940, 171).

TABLE II.

Values for the six-carbon ring from cyclo*hexane compounds.*

	P.	R_C.	R_D.	R_F.	$R_{C'}$.	$Mn_D^{20°}$.
*cyclo*Hexane	1·8	−0·12	−0·11	−0·12	−0·12	−3·72
Methyl*cyclo*hexane	1·3	−0·03	−0·01	−0·01	−0·04	−4·34
Di*cyclo*hexyl	0·8	−0·18	−0·19	−0·19	−0·20	−3·20
*cyclo*Hexene	1·5	−0·27	−0·27	−0·28	−0·30	−3·43
*cyclo*Hexanol *	—	−0·16	−0·17	−0·16	−0·17	−3·19
*cyclo*Hexyl methyl ether	1·5	−0·18	−0·18	−0·18	−0·20	−3·66
*cyclo*Hexyl ethyl ether	0·5	−0·13	−0·16	−0·18	−0·15	−3·54
*cyclo*Hexyl formate	1·3	−0·22	−0·22	−0·21	−0·25	−3·34
*cyclo*Hexyl acetate	2·7	−0·07	−0·08	−0·07	−0·08	−3·34
Mean	1·4	−0·15	−0·15	−0·16	−0·17	−3·53
*cyclo*Hexanone	6·1	−0·10	−0·11	−0·10	−0·12	−3·13
2-Methyl*cyclo*hexanone	4·7	0·08	0·08	0·09	0·07	−3·85
3-Methyl*cyclo*hexanone	2·6	−0·08	−0·07	−0·06	−0·08	−3·79
	6·6	0·19	0·21	0·22	0·21	−3·60
4-Methyl*cyclo*hexanone	5·4	0·22	0·22	0·23	0·23	−3·88
*cyclo*Hexyl chloride	5·8	0·31	0·31	0·31	0·29	−2·95
*cyclo*Hexyl bromide	2·7	0·06	0·07	0·08	0·06	−0·28
*cyclo*Hexyl iodide	2·7	0·22	0·24	0·29	0·30	3·46

* The experimental data for *cyclo*hexanol (Part III, *J.*, 1938, 1331) require revision as follows: M 100·16; $Mn_D^{20°}$ 146·83; $d_4^{20°}$ 0·9515 (supercooled), $d_4^{25°}$ 0·9475, $d_4^{61·8°}$ 0·9178, $d_4^{85·8°}$ 0·8975.

The data for *cyclo*heptane and *cyclo*heptene (Part III, *loc. cit.*) provide the following preliminary values for the constants of the seven-carbon ring :

	P.	R_C.	R_D.	R_F.	$R_{C'}$.	$Mn_D^{20°}$.
*cyclo*Heptane	−1·3	−0·36	−0·35	−0·34	−0·39	−2·40
*cyclo*Heptene	−0·4	−0·29	−0·30	−0·28	−0·30	−3·02

Experimental.

cyclo*Pentyl ethyl ether*. 15·5 G. of sodium were "molecularised" under xylene, the xylene replaced by 150 ml. of anhydrous ether, and a solution of 57 g. of *cyclo*pentanol (b. p. 141—142°/769 mm.) in 75 ml. of dry ether added with stirring during 3 hours, and the whole allowed to stand for 12 hours. 103 G. of pure ethyl iodide were added during 2 hours to the resulting solid sodio-compound : the ether boiled gently. After standing overnight, the ether was removed on a water-bath, and the residue distilled from an air-bath; the crude ether was collected at 120—130° (45 g.). Repeated distillation from sodium to constant physical properties yielded 26 g. of pure *cyclo*pentyl ethyl ether, b. p. 122·5°/763 mm.

cyclo*Pentyl methyl ether*. This was prepared similarly, 97 g. of methyl iodide being used. The yield of the pure cyclo*pentyl methyl ether*, b. p. 105°/763 mm., was 21 g. (Found : C, 72·0; H, 12·1. $C_6H_{12}O$ requires C, 72·2; H, 11·9%).

cyclo*Hexyl methyl ether*. The yield of this ether, b. p. 133·5°/762 mm., from 15·5 g. of "molecular" sodium in 100 ml. of dry ether, 66 g. of pure *cyclo*hexanol in 200 ml. of dry ether, and 97 g. of methyl iodide was 20 g.

cyclo*Hexyl ethyl ether*. This was prepared as for the methyl ether but from 108 g. of ethyl iodide; b. p. 148·5—149·5°/763 mm., yield, 27 g.

cyclo*Hexyl acetate*. Attempts to prepare this ester by refluxing a mixture of 50 g. of *cyclo*hexanol, 90 g. of glacial acetic acid, and 4 g. of concentrated sulphuric acid gave a product of b. p. 160—195°. The fractionation of B.D.H. "pure" *cyclo*hexyl acetate yielded a middle fraction, b. p. 161°/770 mm., $d_4^{20°}$ 0·9609, $n_D^{20°}$ 1·4435, whence R_D 39·27; this was evidently impure and contained free *cyclo*hexanol. The pure ester was readily prepared by making use of the experimental fact that hydrogen chloride dissolves in *cyclo*hexanol without the formation of any appreciable quantity of *cyclo*hexyl chloride. 75 G. of pure *cyclo*hexanol were treated with dry hydrogen chloride until 1·5 g. were absorbed, 135 g. of A.R. glacial acetic acid were added, and the mixture was refluxed for 14 hours. The product was poured into excess of water, the ester layer separated and washed successively with water, saturated sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and fractionated. The yield of *cyclo*hexyl acetate, b. p. 172°/752 mm., was 57 g.

cyclo*Hexyl formate*. When a mixture of 50 g. of pure *cyclo*hexanol and 70 g. of A.R. 98/100% formic acid was refluxed for 6 hours, the product, isolated in the usual way, had b. p. 160—170°. Fractionation of B.D.H. "pure" *cyclo*hexyl formate gave a large middle fraction of b. p. 172·5°/772 mm., $d_4^{20°}$ 0·9872, $n_D^{20°}$ 1·4437, whence R_D 34·47. The pure ester was prepared by refluxing a mixture of 75 g. of pure *cyclo*hexanol containing 1·5 g. of dissolved hydrogen chloride and 103 g. of A.R. 98/100% formic acid for 14 hours, pouring the mixture into excess of concentrated calcium chloride solution (to facilitate separation of the crude ester), and working up as for *cyclo*hexyl acetate. After about 6 g. of *cyclo*hexene had passed over, pure *cyclo*hexyl formate distilled at 159·5—160°/757 mm.; yield, 57 g.

cyclo*Pentyl formate*. This was prepared by refluxing a mixture of 43 g. of distilled *cyclo*pentanol containing 1 g. of dissolved hydrogen chloride and 69 g. of pure A.R. formic acid for 14 hours; after working up as detailed for *cyclo*hexyl formate and fractionating through a Widmer column 26 g. of the pure ester, b. p. 138°/762 mm., were obtained.

cyclo*Pentyl acetate*. This was prepared as for *cyclo*pentyl formate, 90 g. of A.R. glacial acetic acid being used instead of formic acid; the yield of ester, b. p. 152·5—153°/760 mm., was 27 g.

cyclo*Hexyl chloride*. A mixture of 150 g. of pure *cyclo*hexanol, 375 ml. of concentrated hydrochloric acid, and 150 g. of anhydrous calcium chloride was refluxed for 16 hours with frequent shaking. The crude chloride layer was separated, washed successively with water, saturated sodium hydrogen carbonate solution, and water, and dried for 24 hours over excess of calcium chloride. The crude dry product was fractionated through a Widmer column : after a low b. p. fraction (*ca.* 6 g.; mainly *cyclo*hexene) had passed over, 102 g. of *cyclo*hexyl chloride were collected at 141—142°/755 mm.

cyclo*Pentyl chloride*. In a 500-ml. three-necked flask, equipped with a mechanical stirrer and reflux condenser, were placed 43 g. of *cyclo*pentanol (b. p. 140·5—141·5°/769 mm.), 125 ml. of concentrated hydrochloric acid, and 50 g. of anhydrous calcium chloride. The mixture was heated, with stirring, at 100° for 1 hour and the product was isolated as for the *cyclo*hexyl compound. The yield of *cyclo*pentyl chloride, b. p. 114—115°/777 mm., was 30 g.

cyclo*Hexyl bromide*. A mixture of 50 g. of pure *cyclo*hexanol and 260 g. of A.R. 47% hydrobromic acid was slowly distilled during 6 hours from a 500-ml. distilling flask. The distillate was diluted with a little water, and the lower layer separated and washed successively with concentrated hydrochloric acid (to remove unchanged alcohol), water, saturated sodium hydrogen carbonate solution, and water, and dried ($CaCl_2$). The resulting crude bromide (69 g.) was fractionated and the pure *cyclo*hexyl bromide collected at 164°/766 mm.

cyclo*Pentyl bromide*. This was prepared from 43 g. of pure *cyclo*pentanol and 260 g. of constant b. p. hydrobromic acid. The crude, dry bromide (60 g.) upon fractionation afforded pure *cyclo*pentyl bromide, b. p. 136·5°/763 mm.

cyclo*Hexyl iodide*. Vogel's procedure (B.P. 565,452, 1944) was adopted. The flask was charged with 81 g. of pure *cyclo*hexanol and 10·2 g. of purified red phosphorus, and the special apparatus with 100 g. of iodine. The *cyclo*hexanol was kept at the b. p. until a few ml. of the solution of iodine in the alcohol had collected; the latter was slowly added to the *cyclo*hexanol–phosphorus mixture. Heat was liberated in the subsequent formation of *cyclo*hexyl iodide and only a minute flame was necessary beneath

the flask to maintain the reaction. After all the iodine had been introduced into the flask, most of the iodide was distilled into the special apparatus. About 70 ml. of water were then added to the contents of the flask, and the distillation continued to remove the remaining iodide. The yield of crude *cyclo*hexyl iodide, after washing successively with water, concentrated hydrochloric acid, water, saturated sodium hydrogen carbonate solution, and water, and drying ($CaCl_2$), was 145 g. Upon distillation under reduced pressure, the *cyclo*hexyl iodide passed over at 81—83°/20 mm.: a middle fraction, b. p. 81·5°/20 mm., was used for the physical measurements. The pale colour was readily removed by shaking with pure silver powder.

cyclo*Pentyl iodide*. A mixture of 43 g. of pure *cyclo*pentanol and 340 g. of constant b. p. hydriodic acid was slowly distilled during 6 hours from a 500-ml. distilling flask. The crude iodide layer (89 g.) was separated, washed with a little sodium hydrogen sulphite solution to remove the dark colour, and then washed and dried as for the preceding iodide. Distillation of the dry product (83 g.) gave colourless *cyclo*pentyl iodide, b. p. 58°/22 mm.

*Di*cyclo*hexyl*. The Eastman Kodak product was shaken mechanically with half its volume of concentrated sulphuric acid, but the latter did not darken. The acid was separated and the hydrocarbon was washed repeatedly with water, dried ($CaCl_2$), and heated for 5 hours with excess of sodium at 110°. After filtration, the hydrocarbon was distilled. It boiled constantly at 233°/750 mm. and had m. p. 4°.

438. cyclo*Pentyl methyl ether*. B. p. 105°/763 mm.; M 100·16; n_C 1·41828, n_D 1·42036, n_F 1·42543, $n_{G'}$ 1·42916; R_C 29·29, R_D 29·42, R_F 29·72, $R_{G'}$ 29·95; $Mn_D^{20°}$ 142·27. Densities determined: $d_{4°}^{20°}$ 0·8624, $d_{4°}^{41·0°}$ 0·8430, $d_{4°}^{61·5°}$ 0·8240, $d_{4°}^{87·8°}$ 0·7972. Apparatus *A*.

(These headings apply to all subsequent tables in this paper.)

t.	H.	$d_{4°}^{t°}$.	γ.	P.	t.	H.	$d_{4°}^{t°}$.	γ.	P.
16·9°	16·51	0·8653	26·75	263·2	41·5°	15·23	0·8425	24·03	263·2
19·1	16·43	0·8632	26·56	263·4	60·1	14·15	0·8253	21·86	262·7
24·4	16·13	0·8583	25·92	263·3				Mean	263·2

439. cyclo*Pentyl ethyl ether*. B. p. 122·5°/766 mm.; M 114·18; n_C 1·42102, n_D 1·42316, n_F 1·42831, $n_{G'}$ 1·43207; R_C 33·95, R_D 34·11, R_F 34·47, $R_{G'}$ 34·73; $Mn_D^{20°}$ 162·50. Densities determined: $d_{4°}^{20°}$ 0·8528, $d_{4°}^{41·0°}$ 0·8334, $d_{4°}^{60·6°}$ 0·8146, $d_{4°}^{86·3°}$ 0·7899. Apparatus *D*.

17·2°	12·55	0·8554	26·51	302·9	40·9°	11·57	0·8335	23·82	302·6
21·3	12·34	0·8516	25·95	302·6	61·1	10·81	0·8141	21·73	302·8
23·7	12·27	0·8493	25·74	302·8	86·7	9·78	0·7895	19·07	302·2
								Mean	302·7

440. cyclo*Pentyl formate*. B. p. 138°/762 mm.; M 114·14; n_C 1·42990, n_D 1·43209, n_F 1·43741, $n_{G'}$ 1·44127; R_C 29·40, R_D 29·53, R_F 29·43, $R_{G'}$ 30·08; $Mn_D^{20°}$ 163·46. Densities determined: $d_{4°}^{20°}$ 1·0026, $d_{4°}^{41·3°}$ 0·9819, $d_{4°}^{60·4°}$ 0·9624, $d_{4°}^{85·3°}$ 0·9368. Apparatus *A*.

15·8°	17·08	1·0068	32·20	270·1	60·7°	15·03	0·9621	27·08	270·6
19·3	17·02	1·0034	31·98	270·5	85·6	13·81	0·9365	24·22	270·4
41·5	15·90	0·9817	29·23	270·2				Mean	270·4

441. cyclo*Pentyl acetate*. B. p. 153°/760 mm.; M 128·17; n_C 1·42962, n_D 1·43178, n_F 1·43708, $n_{G'}$ 1·44094; R_C 33·92, R_D 34·07, R_F 34·43, $R_{G'}$ 34·70; $Mn_D^{20°}$ 183·51. Densities determined: $d_{4°}^{20°}$ 0·9753, $d_{4°}^{40·7°}$ 0·9540, $d_{4°}^{60·1°}$ 0·9350, $d_{4°}^{86·6°}$ 0·9086. Apparatus *D*.

20·4°	12·74	0·9749	30·67	309·4	60·9°	11·24	0·9342	25·93	309·6
41·4	11·92	0·9533	28·06	309·4	86·1	10·30	0·9091	23·12	309·2
								Mean	309·4

442. cyclo*Pentyl chloride*. B. p. 114·5—115°/777 mm.; M 104·58; n_C 1·44894, n_D 1·45127, n_F 1·45703, $n_{G'}$ 1·46125; R_C 27·83, R_D 27·96, R_F 28·27, $R_{G'}$ 28·50; $Mn_D^{20°}$ 151·78. Densities determined: $d_{4°}^{20°}$ 1·0053, $d_{4°}^{40·1°}$ 0·9855, $d_{4°}^{61·7°}$ 0·9646, $d_{4°}^{86·1°}$ 0·9390. Apparatus *A*.

15·0°	16·40	1·0103	31·03	244·3	40·7°	15·14	0·9849	27·92	244·1
20·5	16·08	1·0048	30·25	244·1	61·3	14·12	0·9650	25·51	243·7
26·6	15·89	0·9987	29·72	244·5	87·0	12·83	0·9381	22·54	243·3
								Mean	244·0

443. cyclo*Pentyl bromide*. B. p. 136·5°/753 mm.; M 149·04; n_C 1·48565, n_D 1·48858, n_F 1·49590, $n_{G'}$ 1·50142; R_C 30·83, R_D 30·99, R_F 31·38, $R_{G'}$ 31·67; $Mn_D^{20°}$ 221·86. Densities determined: $d_{4°}^{20°}$ 1·3873, $d_{4°}^{40·8°}$ 1·3603, $d_{4°}^{60·8°}$ 1·3348, $d_{4°}^{88·1°}$ 1·2983. Apparatus *D*.

16·9°	9·84	1·3913	33·81	258·3	61·1°	8·62	1·3343	28·40	257·9
20·5	9·70	1·3866	33·22	258·0	86·5	7·97	1·3004	25·60	257·8
40·5	9·17	1·3608	30·82	258·1				Mean	258·0

444. cyclo*Pentyl iodide*. B. p. 58°/22 mm.; M 196·04; n_C 1·54268, n_D 1·54705, n_F 1·55817, $n_{G'}$ 1·56700; R_C 36·13, R_D 36·38, R_F 36·99, $R_{G'}$ 37·47; $Mn_D^{20°}$ 303·29. Densities determined: $d_{4°}^{20°}$ 1·7092, $d_{4°}^{40·6°}$ 1·6794, $d_{4°}^{60·5°}$ 1·6498, $d_{4°}^{86·9°}$ 1·6117. Apparatus *D*.

14·9°	8·68	1·7166	36·80	281·3	61·1°	7·74	1·6489	31·52	281·7
20·0	8·58	1·7092	36·21	281·4	85·6	7·23	1·6097	28·74	282·0
42·0	8·12	1·6771	33·63	281·5				Mean	281·6

445. *Di*cyclo*hexyl*. B. p. 233°/750 mm., m. p. 4°; M 166·30; n_C 1·47696, n_D 1·47954, n_F 1·48538, $n_{G'}$ 1·48993; R_C 52·99, R_D 53·22, R_F 53·78, $R_{G'}$ 54·21; $Mn_D^{20°}$ 246·04. Densities determined: $d_4^{20°}$ 0·8868, $d_4^{40·1°}$ 0·8727, $d_4^{60·7°}$ 0·8585, $d_4^{85·0°}$ 0·8420. Apparatus *E*.

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
15·9°	16·04	0·8897	33·24	448·8	60·4°	14·46	0·8587	28·92	449·1
20·5	15·83	0·8864	32·68	448·6	86·7	13·50	0·8408	26·44	448·5
41·2	15·05	0·8720	30·56	448·4				Mean	448·7

446. cyclo*Hexyl methyl ether*. B. p. 133·5°/763 mm.; M 114·18; n_C 1·43248, n_D 1·43470, n_F 1·44004, $n_{G'}$ 1·44398; R_C 33·87, R_D 34·02, R_F 34·38, $R_{G'}$ 34·65; $Mn_D^{20°}$ 163·81. Densities determined: $d_4^{20°}$ 0·8752, $d_4^{40·5°}$ 0·8574, $d_4^{61·9°}$ 0·8395, $d_4^{86·7°}$ 0·8168. Apparatus *D*.

14·7°	13·26	0·8798	28·81	300·7	41·3°	12·19	0·8567	25·79	300·4
17·9	13·14	0·8770	28·46	300·7	60·8	11·42	0·8404	23·70	299·8
27·4	12·77	0·8688	27·40	300·7	86·0	10·41	0·8162	20·98	299·4
								Mean	300·3

447. cyclo*Hexyl ethyl ether*. B. p. 148·5—149·5°/763 mm.; M 128·21; n_C 1·43284, n_D 1·43505, n_F 1·44042, $n_{G'}$ 1·44506; R_C 38·55, R_D 38·73, R_F 39·14, $R_{G'}$ 39·50; $Mn_D^{20°}$ 183·99. Densities determined: $d_4^{20°}$ 0·8640, $d_4^{41·6°}$ 0·8466, $d_4^{60·1°}$ 0·8295, $d_4^{85·3°}$ 0·8074. Apparatus *A*.

17·3°	16·92	0·8663	27·45	338·7	40·6°	15·91	0·8475	25·25	339·1
20·7	16·85	0·8634	27·24	339·2	60·9	14·84	0·8288	23·03	338·9
27·6	16·55	0·8585	26·60	339·2	85·4	13·63	0·8073	20·60	338·4
								Mean	338·9

448. cyclo*Hexyl formate*. B. p. 160°/757 mm.; M 128·17; n_C 1·44073, n_D 1·44305, n_F 1·44857, $n_{G'}$ 1·45263; R_C 34·03, R_D 34·19, R_F 34·56, $R_{G'}$ 34·82; $Mn_D^{20°}$ 184·96. Densities determined: $d_4^{20°}$ 0·9941, $d_4^{41·3°}$ 0·9735, $d_4^{61·1°}$ 0·9552, $d_4^{87·1°}$ 0·9317. Apparatus *A*.

13·0°	17·62	1·0007	33·02	307·0	61·3°	15·38	0·9550	27·50	307·3
19·0	17·39	0·9950	32·40	307·3	87·1	14·25	0·9317	24·86	307·2
41·0	16·35	0·9738	29·81	307·6				Mean	307·3

449. cyclo*Hexyl acetate*. B. p. 172°/752 mm.; M 142·19; n_C 1·43950, n_D 1·44174, n_F 1·44718, $n_{G'}$ 1·45118; R_C 38·61, R_D 38·77, R_F 39·19, $R_{G'}$ 39·50; $Mn_D^{20°}$ 205·00. Densities determined: $d_4^{20°}$ 0·9697, $d_4^{40·9°}$ 0·9501, $d_4^{62·3°}$ 0·9298, $d_4^{86·6°}$ 0·9072. Apparatus *D*.

20·3°	13·08	0·9694	31·31	347·0	61·5°	11·57	0·9306	26·59	347·0
41·1	12·31	0·9496	28·87	347·1	87·1	10·66	0·9067	23·87	346·6
								Mean	346·9

450. cyclo*Hexyl chloride*. B. p. 142°/755 mm.; M 118·61; n_C 1·45993, n_D 1·46235, n_F 1·46828, $n_{G'}$ 1·47266; R_C 32·84, R_D 32·99, R_F 33·35, $R_{G'}$ 33·62; $Mn_D^{20°}$ 173·46. Densities determined: $d_4^{20°}$ 0·9891, $d_4^{40·6°}$ 0·9690, $d_4^{61·0°}$ 0·9497, $d_4^{85·5°}$ 0·9256. Apparatus *A*.

15·9°	17·34	0·9932	32·25	284·6	60·9°	15·24	0·9498	27·10	284·9
40·0	16·20	0·9696	29·41	284·9	86·0	14·16	0·9251	24·53	285·3
								Mean	284·9

451. cyclo*Hexyl bromide*. B. p. 164°/766 mm.; M 163·07; n_C 1·49226, n_D 1·49526, n_F 1·50269, $n_{G'}$ 1·50830; R_C 35·43, R_D 35·61, R_F 36·06, $R_{G'}$ 36·40; $Mn_D^{20°}$ 243·84. Densities determined: $d_4^{20°}$ 1·3360, $d_4^{42·5°}$ 1·3092, $d_4^{61·7°}$ 1·2875, $d_4^{85·7°}$ 1·2583. Apparatus *A*.

23·1°	13·45	1·3323	33·55	294·6	60·6°	12·18	1·2888	29·39	294·6
41·2	12·84	1·3107	31·51	294·8	86·3	11·27	1·2577	26·48	294·4
								Mean	294·6

452. cyclo*Hexyl iodide*. B. p. 81·5°/20 mm.; M 210·07; n_C 1·54333, n_D 1·54765, n_F 1·55856, $n_{G'}$ 1·56730; R_C 40·78, R_D 41·05, R_F 41·73, $R_{G'}$ 42·26; $Mn_D^{20°}$ 325·13. Densities determined: $d_4^{20°}$ 1·6244, $d_4^{41·2°}$ 1·5968, $d_4^{62·2°}$ 1·5702, $d_4^{86·3°}$ 1·5403. Apparatus *D*.

15·2°	9·17	1·6306	36·93	317·6	61·2°	8·19	1·5715	31·06	315·6
25·0	8·92	1·6180	35·64	317·2	86·8	7·66	1·5397	29·13	317·0
40·5	8·65	1·5977	34·13	317·8				Mean	317·1

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366. *Physical Properties and Chemical Constitution. Part XX. Aliphatic Alcohols and Acids.*

By ARTHUR I. VOGEL.

The refractivities at 20° and the parachors of a number of alcohols and aliphatic acids have been determined. Subtraction of the constants for alkyl groups (Part XI, this vol., p. 610) lead to the following mean values for the contributions of the OH and the CO_2H group:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
OH	30·2	2·536	2·546	2·570	2·588	23·94
CO_2H	73·7	7·191	7·226	7·308	7·368	63·98

Summation of the constants for CO (Part XI, *loc. cit.*) and OH gives values approximately equal to those determined directly for CO_2H; this is in contrast to COO (esters), the constants of which are very different from those deduced from CO (ketones) + O (ethers) (Part XII, this vol., p. 624).

Contrary to Sugden's views (" The Parachor and Valency ", 1930, p. 167) no " negative anomaly " of the parachor nor its steady decrease with temperature over the normal temperature range studied could be detected; it is improbable, therefore, that the parachor can be employed to detect association in aliphatic alcohols and acids.

THE objects of the present investigation were: (*a*) The direct determination of the contributions of the OH and the CO_2H group to the parachor and refractivities. (*b*) A comparison of the constants calculated from {CO (Part XI, *loc. cit.*) + OH} with those determined directly for CO_2H. Eisenlohr (*Z. physikal. Chem.*, **1911**, **75**, 585; " Spektrochemie organischer Verbindungen: Molekularrefraktion und -dispersion ", Ferdinand Enke, **1912**, p. 48) computed the refractivity constants for " carbonyl oxygen " O″ from aldehydes and ketones, $C_nH_{2n}O'' - [CH_2]_n$, and for " hydroxyl oxygen " O′ from acids, $C_nH_{2n}O''O' - [CH_2]_n$. It seems surprising, that although the refractivities for some 10 aliphatic alcohols $C_nH_{2n+2}O'$ are collected (*loc. cit.*, p. 590), yet these figures are not employed for the calculation of the constants for " hydroxyl oxygen " but merely for the evaluation of the CH_2 constants and for H (from $C_nH_{2n+2}O' - [CH_2]_n - O'$). Eisenlohr's figures for CH_2 differ considerably from the author's (compare Part IX, *J.*, 1946, 133), and in consequence all the derived constants are subject to appreciable error.

Sugden (*op. cit.*, p. 167; *J.*, 1924, **125**, 38, 1185) utilises the so-called " negative anomaly " between the observed and the predicted value of the parachor and its steady decrease with rise of temperature as evidence for the association of the lower aliphatic alcohols and acids. The results for methyl alcohol, ethyl alcohol, and acetic acid quoted by Sugden in support of this view cover a range of temperatures approaching that of the critical temperature; furthermore, Sugden (*op. cit.*, p. 36) agrees that at high temperatures both the surface tensions and the densities are difficult to measure with accuracy. The author's own parachor determinations of the lower aliphatic alcohols and acids extending to temperatures within 20—25° of the boiling point do not reveal any such " negative anomaly ": the use of the parachor in the detection of association must therefore be accepted with considerable reserve.

The constants for OH have been deduced from the author's own measurements upon aliphatic alcohols by subtracting the values for the alkyl groups (Part XI, *loc. cit.*). The constants for the *n*-nonyl, *n*-decyl, and *n*-undecyl groups have been evaluated from the corresponding hydrocarbons (Part IX, *loc. cit.*), *e.g.*, $n\text{-}C_9H_{20} - H$; $R_{G'}$ for *n*-nonane appears to be slightly in error and the value has been deduced from $C_8H_{17}{}^a + CH_2$. The parachor values are not given for those compounds which give erratic surface tensions by the method of capillary rise.

It will be observed that, unlike most other homologous series, the first member of the series and the secondary alcohol (*iso*propyl alcohol) do not give abnormally high values; they have accordingly been included in the calculation of the mean values. The results for methyl cellosolve, cellosolve, and butyl cellosolve, computed from the relationship

$$OH = Alkyl{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}OH - \{Alkyl + 2CH_2 + O \text{ (in ethers)}\}$$

fall into line. For purposes of comparison the figures deduced for benzyl alcohol and 2-phenylethyl alcohol are included in Table I: the constants for $C_6H_5{\cdot}CH_2$ were calculated from $C_6H_5{\cdot}CH_2Cl$ (XIV, **261**) − Cl, and $C_6H_5{\cdot}CH_2{\cdot}CH_2$ was assumed to be $C_6H_5{\cdot}CH_2 + CH_2$.

The refractivities at 20° and, wherever possible, the parachors of a number of aliphatic carboxylic acids have been determined, and the contributions of the CO_2H group calculated by subtracting the constants for the alkyl groups. The results are summarised in Table II: the

TABLE I.

Values for the OH *group in alcohols.*

Alcohol.	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$
MeOH	32·8	2·54	2·57	2·58	2·61	24·44
EtOH	31·4	2·58	2·60	2·63	2·65	24·00
Pr^{n}OH	29·7	2·56	2·57	2·60	2·62	24·07
Pr^{i}OH	30·6	2·59	2·60	2·62	2·64	23·80
Bu^{n}OH	30·0	2·54	2·55	2·57	2·58	23·91
Bu^{i}OH	28·8	2·54	2·55	2·57	2·58	23·89
Am^{n}OH	29·2	2·58	2·59	2·61	2·63	23·83
Am^{i}OH (synthetic)	—	2·54	2·56	2·58	2·59	23·88
C_6H_{13}·OH	—	2·52	2·53	2·57	2·57	23·80
C_7H_{15}·OH	—	2·48	2·49	2·51	2·53	23·66
C_8H_{17}·OH	—	2·52	2·53	2·57	2·60	23·79
C_9H_{19}·OH	—	2·56	2·55	2·59	2·60	23·73
$C_{10}H_{21}$·OH	—	2·53	2·53	2·54	2·56	23·89
$C_{11}H_{23}$·OH	—	2·51	2·52	2·54	2·56	23·90
C_3H_5·OH	29·4	2·45	2·46	2·47	2·49	24·45
Mean OH	30·2	2·536	2·546	2·570	2·588	23·94
MeO·CH_2·CH_2·OH	31·8	2·45	2·45	2·47	2·48	24·69
EtO·CH_2·CH_2·OH	30·2	2·53	2·54	2·54	2·56	24·29
Bu^{n}O·CH_2·CH_2·OH	—	2·51	2·50	2·53	2·54	23·91
Ph·CH_2·OH	—	2·28	2·28	2·28	2·26	21·65
Ph·CH_2·CH_2·OH	34·0	2·30	2·28	2·29	2·27	22·16

constants for acetic acid have been omitted in the calculation of the mean values. The parachor results are in good agreement with those of Hunter and Maass (*J. Amer. Chem. Soc.*, 1929, **51**, 153); their "experimental values of the parachors were the average obtained over 80° temperature range" over which the variation was less than 1%.

TABLE II.

Values for the CO_2H *group in aliphatic carboxylic acids.*

Acid.	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Me·CO_2H *	76·0	7·29	7·34	7·42	7·49	64·23
Et·CO_2H	74·1	7·17	7·21	7·29	7·36	63·97
Pr^n·CO_2H	73·8	7·21	7·25	7·33	7·39	63·89
Pr^i·CO_2H	74·0	7·16	7·19	7·26	7·33	63·74
Bu^n·CO_2H	73·2	7·21	7·24	7·33	7·38	63·99
Bu^i·CO_2H	73·5	7·19	7·23	7·31	7·37	63·78
Am^n·CO_2H	—	7·20	7·23	7·30	7·37	64·06
C_6H_{13}·CO_2H	—	7·19	7·22	7·32	7·37	64·22
C_7H_{15}·CO_2H	—	7·20	7·24	7·32	7·37	64·15
Mean CO_2H (excluding *)	73·7	7·191	7·226	7·308	7·368	63·98

It is of interest to compare the above mean values for CO_2H with those obtained by the summation of CO (Part XI, *loc. cit.*; the mean values of CO deduced from all the ketones were used) and OH. The results are:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
CO + OH	75·3	7·180	7·214	7·293	7·360	66·33

The difference in the parachor is 1·6 units; the agreement between the refractivities must be regarded as fairly satisfactory in view of the slight variation of the individual CO constants (compare Part XI, *loc. cit.*). These results should be compared with those for COO in esters, the values for which differ considerably from those computed from CO (ketones) + O (ethers) (Part XIII, *loc. cit.*).

If the values for H deduced from CH_2 in aliphatic hydrocarbons (Part IX, *loc. cit.*) are subtracted from those found for OH, the following constants for O (hydroxyl) are obtained:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
O (in OH; Vogel)	14·7	1·510	1·518	1·527	1·548	26·50
O (in OH; Eisenlohr)	—	1·522	1·525	1·531	1·541	—

The agreement of the refractivities with Eisenlohr's figures would seem to be fortuitous owing to his use of what must now be regarded as approximate values for CH_2. These values differ from the constants for O (ethers) and O (acetals) (Part XII, this vol., p. 616).

Added October 14th, 1948.—The author is now of the opinion that two series of values for the constants of CO in ketones are required. The following mean values have been deduced from the date given in Part XI (this vol., p. 611; Table II).

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
CO (in ketones)	44·4	4·579	4·601	4·654	4·702	42·41
CO (in methyl ketones)	46·7	4·730	4·758	4·814	4·874	42·42

If the former constants are employed, the results for CO + OH are:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
CO + OH	74·6	7·115	7·147	7·224	7·290	66·35

Experimental.

Methyl alcohol. One litre of Burrough's synthetic absolute methyl alcohol was dried by Lund and Bjerrum's method (*Ber.*, 1931, **64**, 210) and carefully fractionated through a three-section Pyrex Young and Thomas column, a middle fraction being collected; b. p. 64·5/766 mm. (In the purification of this and the other alcohols precautions were taken to prevent the entrance of moisture; similar precautions were taken during the actual physical measurements.)

Ethyl alcohol. One litre of Burrough's absolute ethyl alcohol was similarly purified; b. p. 78°/760 mm.

The following nine alcohols were dried (A.R. K_2CO_3) and fractionated.

n-*Propyl alcohol.* Redistilled Bisol *n*-propyl alcohol, b. p. 96·5—97°/760 mm., gave b. p. 96·5°/764 mm.

iso*Propyl alcohol.* Redistilled Bisol *iso*propyl alcohol, b. p. 82·1—82·4°/760 mm., gave b. p. 82·3°/760 mm.

n-*Butyl alcohol.* Redistilled Bisol *n*-butyl alcohol, b. p. 117·0—117·2°/750 mm., gave b. p. 117°/754 mm.

iso*Butyl alcohol.* Redistilled Bisol product, b. p. 106—108°/752 mm., gave b. p. 107·5°/752 mm.

n-*Amyl alcohol.* Boots synthetic *n*-amyl alcohol gave alcohol of b. p. 136°/746 mm.

iso*Amyl alcohol.* Sharples synthetic *iso*butylcarbinol afforded alcohol of b. p. 130°/746 mm.

iso*Amyl alcohol.* Bisol fermentation *iso*amyl alcohol finally had b. p. 130·5°/764 mm. The physical properties varied slightly from sample to sample, and hence were not employed in the calculation of the OH constants.

n-*Hexyl alcohol.* The redistilled Carbon and Carbide Corporation product, b. p. 156—157°/752 mm., was purified to b. p. 155·5°/736 mm.

n-*Heptyl alcohol.* A large sample, b. p. 175—177°/771 mm., prepared by reduction of redistilled *n*-heptaldehyde with iron and acetic acid (*Org. Synth.*, 1926, **6**, 52), ultimately had b. p. 175°/764 mm.

The starting material for the next four alcohols was the Deutsche Hydrierwerke product.

n-*Octyl alcohol.* About 250 g. were carefully fractionated, and a middle fraction collected; b. p. 193·5°/764 mm.

n-*Nonyl alcohol.* The alcohol was dried, twice distilled, and a middle fraction collected; b. p. 212°/765 mm.

n-*Decyl and* n-*undecyl alcohol.* The dried product was twice distilled, and a middle sample taken; b. p. 229°/760 mm. and 243·5°/769 mm., respectively.

Allyl alcohol. The B.D.H. pure product was dried (A.R. K_2CO_3) and fractionated through a three-section Pyrex Young and Thomas column; b. p. 97°/760 mm.

The initial alcohol in the following three cases was a Carbon and Carbide Corporation product.

"*Methyl cellosolve*" (*2-methoxyethyl alcohol*). The alcohol was dried (A.R. K_2CO_3) and distilled in an all-glass apparatus through a lagged Widmer column; b. p. 124°/757 mm.

"*Cellosolve*" (*2-ethoxyethyl alcohol*). This was similarly purified; b. p. 135°/761 mm.

"*Butyl cellosolve*" (*2-butoxyethyl alcohol*). This was dried (A.R. K_2CO_3,) fractionated through a well-lagged all-glass Dufton column, and then distilled in an all-glass apparatus; b. p. 168°/754 mm.

Benzyl alcohol. The B.D.H. pure product was dried (K_2CO_3) and fractionated; b. p. 203°/754 mm.

2-Phenylethyl alcohol. A pure commercial product was dried and fractionally distilled; b. p. 216·5°/755 mm.

Tetrahydrofurfuryl alcohol. The B.D.H. product was dried ($CaSO_4$) and carefully fractionated; b. p. 176°/762 mm.

Acetic acid. The procedure employed is based upon that described by Bousfield and Lowry (*J.*, 1911, **99**, 1432). 200 G. of B.D.H. A.R. glacial acetic acid were mixed with 4 g. of A.R. potassium permanganate and distilled from a 250-ml. round-bottomed flask through a three-section Pyrex Young and Thomas column, precautions being taken to prevent ingress of moisture: more than one-third distilled below 116·5°, the remainder at 117·0°, thus proving that purification by direct distillation with potassium permanganate is unsatisfactory. About 600 g. of A.R. glacial acetic acid were partly frozen, and *ca.* 300 g. of liquid poured off. The residual 300 g. was melted, mixed with 6 g. of A.R. potassium permanganate and fractionally distilled as before. The fraction, b. p. 116·5—117·5°/765 mm. (*ca.* 225 g.), was collected, partly frozen and about half of the fluid portion rejected. Repetition of the distillation afforded pure acetic acid of b. p. 118·0°/765 mm.

Propionic acid. About 1 l. of Boake Roberts commercial acid were dried (Na_2SO_4) and fractionated through a three-section Pyrex Young and Thomas column, that boiling at 139—141°/760 mm. (mainly 140·8—141·0°) being collected separately. 300 G. of this redistilled acid were mixed with 6 g. of A.R. potassium permanganate and fractionated as before; the first half was rejected, and the remainder distilled constantly at 140·7°/760 mm., from which a middle fraction was separated for the physical measurements.

n-*Butyric acid.* 250 G. of the redistilled commercial product, b. p. 161·5—163°/756 mm., were mixed with 5 g. of A.R. potassium permanganate and fractionated as before. The first third was discarded, and the remainder distilled constantly at 162·5°/767 mm.

iso*Butyric acid.* About 500 g. of Hopkin and Williams pure acid were dried (Na_2SO_4) and fractionally distilled through a two-section Pyrex Young and Thomas column. After a small fraction of low b. p. had passed over, the acid boiled constantly at 154·5°/775 mm., from which a middle fraction was set aside for the physical measurements.

n-*Valeric acid.* This acid was synthesised in quantity according to the scheme: *n*-Butyl bromide ⟶ *n*-butyl cyanide ⟶ *n*-valeric acid. A large sample was distilled, and a middle fraction, b. p. 184°/768 mm., was collected.

iso*Valeric acid.* About 500 g. of Kahlbaum's pure acid was dried (Na_2SO_4) and fractionally distilled as before; b. p. 176·5°/762 mm.

n-*Hexoic acid.* Boots pure acid was dried and redistilled; b. p. 203°/756 mm.

n-*Heptoic acid.* A large commercial sample was dried and twice fractionated; b. p. 222°/764 mm.

n-*Octoic acid.* The redistilled Deutsche Hydrierwerke product, b. p. 235·5—238°/762 mm., was carefully fractionated; b. p. 236°/769 mm.

453. *Methyl alcohol.* B. p. 64·5°/766 mm.; *M* 32·04; n_C 1·32694, n_D 1·32855, n_F 1·33225, $n_{G'}$ 1·33477; R_C 8·18, R_D 8·22, R_F 8·30, $R_{G'}$ 8·36; $Mn_D^{20°}$ 42·57. Densities determined: $d_4^{20°}$ 0·7924, $d_4^{40·9°}$ 0·7727. Apparatus *A*.

(These headings apply to all subsequent tables in this paper.)

t.	*H.*	$d_4^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_4^{t°}$.	*γ.*	*P.*
15·2°	15·33	0·7969	22·88	87·9	28·2°	14·86	0·7847	21·83	88·3
19·0	15·21	0·7934	22·60	88·0	40·2	14·38	0·7733	20·96	88·7
								Mean	88·2

454. *Ethyl alcohol.* B. p. 78°/760 mm.; *M* 46·07; n_C 1·35959, n_D 1·36139, n_F 1·36565, $n_{G'}$ 1·36855; R_C 12·84, R_D 12·90, R_F 13·04, $R_{G'}$ 13·13; $Mn_D^{20°}$ 62·72. Densities determined: $d_4^{20°}$ 0·7910, $d_4^{41·3°}$ 0·7735, $d_4^{97·2°}$ 0·7597. Apparatus *A*.

16·8°	15·18	0·7937	22·56	126·5	40·3°	14·32	0·7743	20·76	127·0
22·3	15·02	0·7891	22·19	126·7	59·3	13·43	0·7580	19·06	127·1
25·8	14·93	0·7862	21·98	126·9				Mean	126·8

455. n-*Propyl alcohol.* B. p. 96·5°/764 mm.; *M* 60·13; n_C 1·38364, n_D 1·38556, n_F 1·39015, $n_{G'}$ 1·39341; R_C 17·46, R_D 17·54, R_F 17·73, $R_{G'}$ 17·86; $Mn_D^{20°}$ 83·32. Densities determined: $d_4^{20°}$ 0·8043, $d_4^{41·6}$ 0·7880, $d_4^{59·4°}$ 0·7745. Apparatus *A*.

17·8°	15·84	0·8060	23·91	165·0	41·6°	14·90	0·7880	21·99	165·3
21·0	15·73	0·8035	23·61	165·0	59·9	14·23	0·7741	20·63	165·7
								Mean	165·2

456. iso*Propyl alcohol.* B. p. 82·3°/760 mm.; *M* 60·09; n_C 1·37523, n_D 1·37711, n_F 1·38168, $n_{G'}$ 1·38484; R_C 17·50, R_D 17·58, R_F 17·77, $R_{G'}$ 17·90; $Mn_D^{20°}$ 82·75. Densities determined: $d_4^{20°}$ 0·7864, $d_4^{41·2°}$ 0·7697, $d_4^{59·2°}$ 0·7532. Apparatus *A*.

17·1°	14·68	0·7888	21·68	164·4	41·9°	13·60	0·7691	19·59	164·4
21·0	14·50	0·7858	21·34	164·3	59·5	12·75	0·7530	17·98	164·5
								Mean	164·4

457. n-*Butyl alcohol.* B. p. 117°/754 mm.; *M* 74·12; n_C 1·39732, n_D 1·39929, n_F 1·40407, $n_{G'}$ 1·40744; R_C 22·04, R_D 22·14, R_F 22·37, $R_{G'}$ 22·53; $Mn_D^{20°}$ 103·72. Densities determined: $d_4^{20°}$ 0·8104, $d_4^{40·4°}$ 0·7956, $d_4^{61·0°}$ 0·7793, $d_4^{85·0°}$ 0·7594. Apparatus *A*.

16·0°	16·91	0·8134	25·76	205·3	61·8°	14·85	0·7787	21·65	205·3
24·0	16·53	0·8074	24·99	205·3	86·5	13·70	0·7582	19·45	205·3
41·9	15·80	0·7945	23·51	205·4				Mean	205·3

458. iso*Butyl alcohol.* B. p. 107·5°/752 mm.; *M* 74·12; n_C 1·39343, n_D 1·39549, n_F 1·40016, $n_{G'}$ 1·40361; R_C 22·07, R_D 22·17, R_F 22·41, $R_{G'}$ 22·57; $Mn_D^{20°}$ 103·43. Densities determined: $d_4^{20°}$ 0·8021, $d_4^{42·7°}$ 0·7852, $d_4^{61·5°}$ 0·7699, $d_4^{85·0°}$ 0·7501. Apparatus *D*.

15·9°	11·69	0·8053	23·25	202·1	61·9°	10·34	0·7696	19·65	202·8
23·2	11·46	0·7996	22·63	202·2	86·5	9·52	0·7489	17·61	202·7
41·3	10·98	0·7863	21·32	202·6				Mean	202·6

459. n-*Amyl alcohol.* B. p. 136°/746 mm.; *M* 88·15; n_C 1·40793, n_D 1·40999, n_F 1·41498, n_G 1·41854; R_C 26·72, R_D 26·84, R_F 27·13, $R_{G'}$ 27·33; $Mn_D^{20°}$ 124·29. Densities determined: $d_4^{20°}$ 0·8136, $d_4^{41·4°}$ 0·7981, $d_4^{60·6°}$ 0·7835, $d_4^{85·0°}$ 0·7640. Apparatus *D*.

14·3°	13·04	0·8178	26·31	244·2	62·2°	11·46	0·7823	22·14	244·4
17·2	12·92	0·8157	26·03	244·1	87·0	10·56	0·7625	19·93	244·1
40·9	12·14	0·7958	23·94	244·2				Mean	244·2

460A. iso*Amyl alcohol* (fermentation; Bisol). B. p. 130·5°/764 mm.; M 88·15; n_C 1·40527, n_D 1·40731, n_F 1·41227, $n_{G'}$ 1·41582; R_C 26·64, R_D 26·75, R_F 27·03, $R_{G'}$ 27·24; $Mn_D^{20°}$ 124·05. Densities determined: $d_{4°}^{2.°}$ 0·8118, $d_{4°}^{42·3°}$ 0·7952, $d_{4°}^{61·4°}$ 0·7813, $d_{4°}^{87·0°}$ 0·7598. Apparatus *D*.

t.	*H.*	$d_{4°}^{t°}$	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$	γ.	*P.*
19·3°	12·07	0·8123	24·21	240·8	60·9°	10·78	0·7817	20·81	240·9
24·3	11·87	0·8085	23·70	240·6	86·5	9·93	0·7602	18·64	240·9
42·3	11·36	0·7952	22·31	240·9					
								Mean	240·8

460B. iso*Amyl alcohol* (synthetic; Sharples). B. p. 130°/746 mm.; n_C 1·40657, n_D 1·40865, n_F 1·41361, $n_{G'}$ 1·41708; R_C 26·64, R_D 26·76, R_F 27·04, $R_{G'}$ 27·24; $Mn_D^{20°}$ 124·18. Densities determined: $d_{4°}^{20°}$ 0·8139, $d_{4°}^{40·0°}$ 0·7994, $d_{4°}^{60·2°}$ 0·7844, $d_{4°}^{86·0°}$ 0·7639.

461. n-*Hexyl alcohol*. B. p. 155·5°/736 mm.; M 102·17; n_C 1·41606, n_D 1·41816, n_F 1·42325, $n_{G'}$ 1·42694; R_C 31·25, R_D 31·39, R_F 31·73, $R_{G'}$ 31·96; $Mn_D^{20°}$ 144·90. Densities determined: $d_{4°}^{20°}$ 0·8205, $d_{4°}^{41·0°}$ 0·8058, $d_{4°}^{61·8°}$ 0·7909, $d_{4°}^{86·4°}$ 0·7713. The surface-tension results by the method of capillary rise were erratic.

462. n-*Heptyl alcohol*. B. p. 175°/764 mm.; M 116·20; n_C 1·42137, n_D 1·42351, n_F 1·42870, $n_{G'}$ 1·43243; R_C 35·88, R_D 36·04, R_F 36·42, $R_{G'}$ 36·70; $Mn_D^{20°}$ 165·41; $d_{4°}^{20°}$ 0·8219.

463. n-*Octyl alcohol*. B. p. 212°/765 mm.; M 144·25; n_C 1·43105, n_D 1·43325, n_F 1·43856, $n_{G'}$ 1·44241; R_C 45·14, R_D 45·34, R_F 45·83, $R_{G'}$ 46·17; $Mn_D^{20°}$ 206·75; $d_{4°}^{20°}$ 0·8273.

464. n-*Nonyl alcohol*. B. p. 212°/765 mm.; M 144·25; n_C 1·43105, n_D 1·43325, n_F 1·43856, $n_{G'}$ 1·44241; R_C 45·14, R_D 45·34, R_F 45·83, $R_{G'}$ 46·17; $Mn_D^{20°}$ 206·75; $d_{4°}^{20°}$ 0·8273.

465. n-*Decyl alcohol*. B. p. 229°/760 mm.; M 158·26; n_C 1·43440, n_D 1·43660, n_F 1·44197, $n_{G'}$ 1·44591; R_C 49·78, R_D 50·00, R_F 50·53, $R_{G'}$ 50·92; $Mn_D^{20°}$ 227·36; $d_{4°}^{20°}$ 0·8287.

466. n-*Undecyl alcohol*. B. p. 243·5°/769 mm.; M 172·30; n_C 1·43697, n_D 1·43918, n_F 1·44460, $n_{G'}$ 1·44859; R_C 54·40, R_D 54·64, R_F 55·22, $R_{G'}$ 55·65; $Mn_D^{20°}$ 247·97; $d_{4°}^{20°}$ 0·8298.

467. *Allyl alcohol*. B. p. 97°/760 mm.; M 58·08; n_C 1·40994, n_D 1·41266, n_F 1·41941, $n_{G'}$ 1·42456; R_C 16·88, R_D 16·98, R_F 17·22, $R_{G'}$ 17·41; $Mn_D^{20°}$ 82·05. Densities determined: $d_{4°}^{20°}$ 0·8524, $d_{4°}^{41·5°}$ 0·8345, $d_{4°}^{61·0°}$ 0·8176. Apparatus *A*.

17·1°	16·25	0·8549	26·01	153·4	41·2°	15·23	0·8348	23·81	153·7
28·5	15·75	0·8452	24·93	153·5	60·2	14·43	0·8183	22·11	154·4
								Mean	153·7

468. 2-*Methoxyethyl alcohol* ("*methyl cellosolve*"). B. p. 124°/757 mm.; M 76·07; n_C 1·40039, n_D 1·40238, n_F 1·40713, $n_{G'}$ 1·41049; R_C 19·10, R_D 19·18, R_F 19·38, $R_{G'}$ 19·52; $Mn_D^{20°}$ 106·68. Densities determined: $d_{4°}^{20°}$ 0·9663, $d_{4°}^{40·9°}$ 0·9465, $d_{4°}^{61·9°}$ 0·9277, $d_{4°}^{86·1°}$ 0·9043. Apparatus *A*.

14·9°	17·50	0·9710	31·82	186·1	61·5°	15·68	0·9281	27·25	187·3
41·0	16·52	0·9464	29·28	187·0	85·6	14·68	0·9048	24·87	187·8
								Mean	187·1

469. 2-*Ethoxyethyl alcohol* ("*cellosolve*"). B. p. 135°/761 mm.; M 90·12; n_C 1·40547, n_D 1·40751, n_F 1·41224, $n_{G'}$ 1·41591; R_C 23·78, R_D 23·89, R_F 24·13, $R_{G'}$ 24·32; $Mn_D^{20°}$ 126·84. Densities determined: $d_{4°}^{20°}$ 0·9297, $d_{4°}^{41·0°}$ 0·9114, $d_{4°}^{60·9°}$ 0·8941, $d_{4°}^{86·4°}$ 0·8713. Apparatus *D*.

24·7°	12·45	0·9255	28·46	224·9	60·3°	11·33	0·8946	25·03	225·3
29·1	12·33	0·9218	28·07	225·0	87·2	10·64	0·8706	22·88	226·4
40·3	11·92	0·9120	26·85	224·9					
								Mean	225·3

470. n-*Butoxyethyl alcohol* ("*butyl cellosolve*"). B. p. 168°/754 mm.; M 118·17; n_C 1·41745, n_D 1·41956, n_F 1·42458, $n_{G'}$ 1·42833; R_C 32·99, R_D 33·13, R_F 33·48, $R_{G'}$ 33·73; $Mn_D^{20°}$ 167·75. Densities determined: $d_{4°}^{20°}$ 0·9018, $d_{4°}^{40·0°}$ 0·8850, $d_{4°}^{60·5°}$ 0·8681, $d_{4°}^{86·4°}$ 0·8457. Apparatus *A*.

17·9°	15·73	0·9036	26·62	297·0	60·1°	14·25	0·8684	23·17	297·9
40·9	15·13	0·8843	25·05	299·0	86·5	13·34	0·8456	21·12	299·4
								Mean	298·3

The surface-tension measurements were not altogether satisfactory and require confirmation by the method of maximum bubble pressure

471. *Benzyl alcohol*. B. p. 203°/754 mm.; M 108·13; n_C 1·53552, n_D 1·54033, n_F 1·55259, $n_{G'}$ 1·56227; R_C 32·22, R_D 32·47, R_F 33·08, $R_{G'}$ 33·56; $Mn_D^{20°}$ 166·55. Densities determined: $d_{4°}^{20°}$ 1·0454, $d_{4°}^{41·1°}$ 1·0301, $d_{4°}^{61·0°}$ 1·0152, $d_{4°}^{86·6°}$ 0·9952. The surface tension results were unsatisfactory.

472. 2-*Phenylethyl alcohol*. B. p. 216·5°/755 mm.; M 122·16; n_C 1·52760, n_D 1·53210, n_F 1·54363, $n_{G'}$ 1·55259; R_C 36·86, R_D 37·12, R_F 37·79, $R_{G'}$ 38·31; $Mn_D^{20°}$ 187·15. Densities determined: $d_{4°}^{20°}$ 1·0198, $d_{4°}^{40·0°}$ 1·0053, $d_{4°}^{60·5°}$ 0·9904, $d_{4°}^{86·4°}$ 0·9701. Apparatus *D*.

24·5°	16·09	1·0165	40·39	303·0	59·5°	14·98	0·9911	36·67	303·3
40·9	15·55	1·0047	38·58	303·0	86·7	14·16	0·9699	33·92	303·9
								Mean	303·3

473. *Tetrahydrofurfuryl alcohol.* B. p. 176°/762 mm.; *M* 102·13, n_C 1·44987, n_D 1·45197, n_F 1·45731, $n_{G'}$ 1·46173; R_C 26·05, R_D 26·15, R_F 26·42, $R_{G'}$ 26·64; $Mn_D^{20°}$ 148·29. Densities determined: $d_{4°}^{20}$ 1·0535, $d_{4°}^{41·3°}$ 1·0365, $d_{4°}^{61·6°}$ 1·0194, $d_{4°}^{86·5°}$ 0·9984. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
21·6°	14·55	1·0522	37·81	240·7	60·5°	13·43	1·0202	33·84	241·4
22·8	14·50	1·0512	37·64	240·7	87·0	12·67	0·9971	31·20	242·1
40·7	14·00	1·0370	35·85	241·0				Mean	241·5

474. *Acetic acid.* B. p. 118·0°/765 mm.; *M* 60·05; n_C 1·36952, n_D 1·37151, n_F 1·37615, $n_{G'}$ 1·37941; R_C 12·93, R_D 12·99, R_F 13·14, $R_{G'}$ 13·24; $Mn_D^{20°}$ 82·36. Densities determined: $d_{4°}^{20°}$ 1·0492, $d_{4°}^{41·4°}$ 1·0267, $d_{4°}^{61·4}$ 1·0044, $d_{4°}^{87·1°}$ 0·9769. Apparatus *D*.

20·1°	10·64	1·0491	27·57	131·2	42·3°	10·01	1·0257	25·36	131·4
23·1	10·55	1·0459	27·25	131·2	61·8	9·46	1·0040	23·46	131·9
26·9	10·48	1·0418	26·96	131·3	87·5	8·65	0·9765	20·86	131·4
								Mean	131·4

475. *Propionic acid.* B. p. 140·7°/760 mm.; *M* 74·08; n_C 1·38425, n_D 1·38623, n_F 1·39098, $n_{G'}$ 1·39430; R_C 17·43, R_D 17·51, R_F 17·70, $R_{G'}$ 17·84; $Mn_D^{20°}$ 102·69. Densities determined: $d_{4°}^{20°}$ 0·9942, $d_{4°}^{42·3°}$ 0·9715, $d_{4°}^{62·1°}$ 0·9510, $d_{4°}^{86·5°}$ 0·9263. Apparatus *A*.

14·6°	14·52	0·9997	27·24	169·2	61·5°	12·65	0·9516	22·54	169·6
26·1	14·13	0·9880	26·14	169·5	86·3	11·62	0·9265	20·16	169·4
42·1	13·42	0·9717	24·42	169·5				Mean	169·4

476. n-*Butyric acid.* B. p. 162·5°/767 mm.; *M* 88·10; n_C 1·39552, n_D 1·39768, n_F 1·40256, $n_{G'}$ 1·40612; R_C 22·11, R_D 22·22, R_F 22·46, $R_{G'}$ 22·63; $Mn_D^{20°}$ 123·14. Densities determined: $d_{4°}^{20°}$ 0·9563, $d_{4°}^{41·2°}$ 0·9373, $d_{4°}^{61·0°}$ 0·9187, $d_{4°}^{86·5°}$ 0·8938. Apparatus *A*.

22·5°	14·70	0·9540	26·26	209·0	42·0	13·96	0·9366	24·48	209·2
24·4	14·64	0·9522	26·10	209·1	61·4	13·20	0·9183	22·70	209·4
29·8	14·46	0·9473	25·65	209·3	87·3	12·15	0·8933	20·32	209·4
								Mean	209·3

477. iso*Butyric acid.* B. p. 154·5°/775 mm.; *M* 88·10; n_C 1·39096, n_D 1·39300, n_F 1·39782, $n_{G'}$ 1·40129; R_C 22·07, R_D 22·17, R_F 22·41, $R_{G'}$ 22·59; $Mn_D^{20°}$ 122·69. Densities determined: $d_{4°}^{20°}$ 0·9483, $d_{4°}^{41·3°}$ 0·9276, $d_{4°}^{60·8°}$ 0·9090, $d_{4°}^{85·2°}$ 0·8843. Apparatus *D*.

15·1°	10·88	0·9531	25·61	207·9	41·8°	10·02	0·9271	22·96	207·8
20·1	10·71	0·9482	25·08	207·9	59·5	9·46	0·9103	21·27	207·9
23·5	10·63	0·9459	24·83	207·8	87·5	8·61	0·8821	18·76	207·6
								Mean	207·8

478. n-*Valeric acid.* B. p. 184°/768 mm.; *M* 102·13; n_C 1·40589, n_D 1·40800, n_F 1·41305, $n_{G'}$ 1·41672; R_C 26·71, R_D 26·83, R_F 27·13, $R_{G'}$ 27·33; $Mn_D^{20°}$ 143·80. Densities determined: $d_{4°}^{20°}$ 0·9390, $d_{4°}^{41·0°}$ 0·9211, $d_{4°}^{60·8°}$ 0·9039, $d_{4°}^{85·5°}$ 0·8819. Apparatus *A*.

19·2°	15·51	0·9397	27·29	248·4	60·4°	13·92	0·9042	23·57	248·7
27·2	15·16	0·9328	26·48	248·4	86·1	12·90	0·8815	21·29	248·9
41·7	14·54	0·9205	25·06	248·2				Mean	248·5

479. iso*Valeric acid.* B. p. 176·5°/762 mm.; *M* 102·13; n_C 1·40123, n_D 1·40331, n_F 1·40832, $n_{G'}$ 1·41188; R_C 26·72, R_D 26·85, R_F 27·15, $R_{G'}$ 27·36; $Mn_D^{20°}$ 143·32. Densities determined: $d_{4°}^{20°}$ 0·9286, $d_{4°}^{40·8°}$ 0·9102, $d_{4°}^{60·8°}$ 0·8926, $d_{4°}^{86·9°}$ 0·8687. Apparatus *D*.

19·9°	11·14	0·9289	25·55	247·2	63·1°	9·87	0·8920	21·74	247·2
26·4	10·96	0·9229	24·98	247·4	85·7	9·17	0·8698	19·70	247·4
43·4	10·39	0·9079	23·30	247·1				Mean	247·3

480. n-*Hexoic acid.* B. p. 203°/756 mm.; *M* 116·16; n_C 1·41412, n_D 1·41626, n_F 1·42143, $n_{G'}$ 1·42516; R_C 31·34, R_D 31·48, R_F 31·82, $R_{G'}$ 32·07; $Mn_D^{20°}$ 164·52; $d_{4°}^{20°}$ 0·9265.

481. n-*Heptoic acid.* B. p. 222°/764 mm.; *M* 130·18; n_C 1·42138, n_D 1·42361, n_F 1·42896, $n_{G'}$ 1·43281; R_C 35·92, R_D 36·08, R_F 36·48, $R_{G'}$ 36·76; $Mn_D^{20°}$ 185·32; $d_{4°}^{20°}$ 0·9200.

482. n-*Octoic acid.* B. p. 236°/769 mm.; *M* 144·21; n_C 1·42557, n_D 1·42777, n_F 1·43311, $n_{G'}$ 1·43693; R_C 40·60, R_D 40·79, R_F 41·23, $R_{G'}$ 41·54; $Mn_D^{20°}$ 205·90; $d_{4°}^{20°}$ 0·9093.

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367. *Physical Properties and Chemical Constitution. Part XXI. Aliphatic Thiols, Sulphides, and Disulphides.*

By Arthur I. Vogel.

New determinations have been made of the refractivities at 20° and the parachors of a series of alkylthiols. By subtracting the constants for alkyl groups (Part XI, this vol., p. 611) the undermentioned values for the SH group are obtained; the constants for S (in thiols) are derived by subtracting the constants for H in CH_2 (Part IX, *J.*, 1946, 133):

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
SH	66·4	8·691	8·757	8·919	9·057	50·20
S (in thiols)	50·7	7·665	7·729	7·876	8·017	52·76

The data for aliphatic sulphides and disulphides of Part VII (*J.*, 1943, 16) lead to the following values for S (in sulphides) and S_2 (in disulphides):

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
S (in sulphides)	48·6	7·852	7·921	8·081	8·233	52·86
S_2 (in disulphides)	97·2	15·914	16·054	16·410	16·702	106·52

New experimental data for phenyl alkyl sulphides are provided; subtraction of the corresponding figures for alkylbenzenes (Part X, this vol., p. 607) leads to constants for S which are generally higher than those in alkyl sulphides.

Price and Twiss (*J.*, 1912, **101**, 1259), utilising Auwers and Eisenlohr's constants for carbon, hydrogen, and oxygen, have deduced the following values for the refractivities of S from their measurements upon dithio-esters of the type $S_2(CHR{\cdot}CO_2R')_2$: R_C 8·07, R_D 8·13, and R_F 8·31. They have also computed *inter alia* from the results of earlier investigators the constants for S in thiols (R_C 7·63, R_D 7·69, R_F 7·83 and $R_{G'}$ 7·98) and in sulphides (R_C 7·85, R_D 7·97, R_F 8·13, $R_{G'}$ 8·28). The parachor for sulphur has been computed by Sugden, Reed, and Wilkins (*J.*, 1925, **127**, 1533) from experimental data described in the literature for sulphur monochloride, carbon disulphide, ethylthiol, and phenylthiol: Sugden's own constants, based upon $CH_2 = 39·0$, were used throughout and a mean value for S of 48·2 was obtained. It would appear that the compounds selected for the deduction of such a fundamental constant, although perhaps inevitable at the time, cannot be regarded as altogether satisfactory in view of their heterogeneous character.

New determinations have been made of the refractivities at 20° and the parachors of a number of thiols, and the contributions of the SH group calculated by direct subtraction of the values for the alkyl groups (Part XI, *loc. cit.*). The results are shown in Table I. The constants for Bu^t were computed from Bu^{t}Cl (VIII, **55**) — Cl (Part XIV, this vol., p. 644). The surface-tension results for *n*-heptyl- and *n*-octyl-thiols determined by the method of capillary rise require confirmation by the method of maximum bubble pressure since these compounds appear to be on the border line of applicability of the former procedure. In consequence, the parachor values may be slightly in error and have not been employed in the calculation of the mean; if the parachors for these two thiols are included, the mean parachor is reduced to 65·9. The constants derived from thiophenol, utilising the values for Ph of Part XV (this vol., p. 654) are given for purposes of reference.

Table I.

Values for SH *from alkylthiols.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Et·SH	66·5	8·65	8·72	8·89	9·04	50·23
Pr^n·SH	66·9	8·68	8·74	8·91	9·05	50·11
Pr^i·SH *	68·0	8·46	8·52	8·67	8·81	49·10
Bu^n·SH	66·1	8·73	8·79	8·95	9·10	50·28
Bu^i·SH	65·9	8·69	8·76	8·91	9·05	50·16
Bu^t·SH *	66·1	8·81	8·88	9·06	9·20	50·32
Am^n·SH	66·1	8·69	8·75	8·90	9·06	50·29
Am^i·SH	66·8	8·68	8·76	8·91	9·05	50·21
$C_6H_{13}^n$·SH	66·2	8·68	8·75	8·93	9·04	50·26
$C_7H_{15}^n$·SH	[64·2]	8·64	8·70	8·86	8·97	50·07
$C_8H_{17}^n$·SH	[64·0]	8·78	8·84	9·01	9·15	50·23
Mean SH (excluding *)	66·4	8·691	8·757	8·919	9·057	50·20
Ph·SH	67·6	9·08	9·16	9·66	—	53·12

The constants for S in dialkyl sulphides have been calculated with the aid of the experimental data recorded in Part VII (*J.*, 1943, 16; compare Strecker and Spitaler, *Ber.*, 1926, **59**, 1754, who

give refractivity data for dimethyl, diethyl, and di-*n*-propyl sulphides which are in moderate agreement with the author's results) and the hydrocarbon values given in Part XI (*loc. cit.*). The results are summarised in Table II; the compounds marked with an asterisk have not been used in the evaluation of the mean values. If all the sulphides containing a methyl group in addition to those marked with an asterisk be omitted from the calculation of the mean values, the mean constants for S (in sulphides) are: P 47·9, R_C 7·888, R_D 7·955, R_F 8·122, R_G 8·260, $Mn_D^{20°}$ 52·86.

TABLE II.

Values for S *from dialkyl sulphides.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	Mn_D^{20}
SMe_2	52·4	7·75	7·82	7·97	8·12	52·94
SMeEt	51·1	7·72	7·80	7·93	8·12	52·83
SEt_2	50·8	7·87	7·93	8·12	8·29	52·64
$SMeBu^n$	48·3	7·76	7·82	7·98	8·21	52·95
$SMeBu^i$	50·4	7·82	7·90	8·04	8·19	52·74
$SMeBu^t$ *	48·3	7·71	7·79	7·94	8·10	54·05
SPr^n_2	48·0	7·80	7·86	8·03	8·17	52·81
SPr^i_2 *	50·3	8·07	8·17	8·30	8·47	52·29
$SEtBu^n$	49·4	7·89	7·96	8·13	8·28	52·80
$SEtBu^i$ *	47·6	7·92	7·97	8·15	8·31	53·76
SBu^n_2	47·7	7·82	7·89	8·04	8·20	52·93
SBu^i_2 *	47·9	7·98	8·05	8·22	8·34	52·58
SBu^s_2 *	52·7	8·24	8·30	8·49	8·64	51·77
SAm^n_2	47·1	7·81	7·88	8·03	8·18	52·96
SAm^i_2	47·8	7·99	8·08	8·24	8·38	52·66
$S(C_6H_{13}{}^n)_2$	46·5	7·96	8·02	8·19	8·33	53·02
$S(C_7H_{15}{}^n)_2$	47·0	7·93	7·99	8·15	8·25	53·08
$S(C_8H_{17}{}^n)_2$	47·0	7·93	7·99	8·15	8·25	53·08
Mean S (excluding *)	48·6	7·852	7·921	8·081	8·233	52·86

New measurements of the refractivities at 20° and the parachors for phenyl alkyl sulphides have been made; the constants for S in these compounds have been computed by direct subtraction of the experimental figures for the alkylbenzenes (Part X, this vol., p. 607). The results are collected in Table III; it will be noted that the refractivities for S are consistently higher than those deduced from dialkyl sulphides.

TABLE III.

Values for S *from phenyl alkyl sulphides.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
SPhMe	50·2	8·23	8·32	8·64	8·92	59·26
SPhEt	50·1	8·32	8·44	8·71	8·92	57·72
$SPhPr^n$	48·3	8·33	8·43	8·79	9·00	57·32
$SPhPr^i$	51·1	8·48	8·59	8·90	9·15	56·25
$SPhBu^n$	48·5	8·40	8·49	8·83	9·10	57·52
$SPhAm^n$	47·3	8·39	8·50	8·81	9·08	57·00
$SPhC_6H_{13}{}^n$	51·6	8·55	8·67	9·01	9·24	56·66
SPh_2	51·4	8·92	9·05	9·48	9·89	60·18

The constants for S_2 in aliphatic disulphides have been computed from the experimental data of Part VII (*J.*, 1943, 16) by subtraction of the values for alkyl groups (Part XI, *loc. cit.*) and are collected in Table IV. In the calculation of the mean values, the constants for $S_2Pr^i_2$ and of S_2Me_2 (which, unlike SMe_2, appears to be abnormal) have been omitted.

TABLE IV.

Values for S_2 *from aliphatic disulphides.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
S_2Me_2 *	103·2	15·70	15·84	16·18	16·51	107·47
S_2Et_2	100·4	15·92	16·07	16·42	16·74	106·77
$S_2Pr^n_2$	97·6	15·84	15·97	16·33	16·64	106·66
$S_2Pr^i_2$ *	100·5	16·09	16·23	16·58	16·89	106·28
$S_2Bu^n_2$	97·2	15·92	16·04	16·39	16·69	106·58
$S_2Am^n_2$	94·7	15·93	16·09	16·44	16·75	106·40
$S_2Am^i_2$	96·1	15·96	16·12	16·47	16·79	106·19
Mean S_2 (excluding *)	97·2	15·914	16·054	16·410	16·702	106·52

The results for sulphur monochloride (*P* 96·0, R_D 17·67, $Mn_D^{20°}$ 112·00) give a reasonable value for the parachor of S_2, but R_D seems high; the latter may be partly due to the difficulty of measurement of the refractive index.

It is of interest to employ the experimental data for the evil-smelling dithio-esters $S_2\{[CH_2]_x{\cdot}CO_2R\}_2$ (Price and Twiss, *loc. cit.*) for the calculation of S_2; these can be obtained directly by subtraction of the refractivities of the appropriate carboxylic esters (Part XIII, this vol., p. 624) and are given below.

S_2 *from Dithio-esters* (Price and Twiss).

	R_C.	R_D.	R_F.
$S_2(CH_2{\cdot}CO_2Me)_2$	16·04	16·17	16·52
$S_2(CH_2{\cdot}CO_2Et)_2$	15·88	16·02	16·37
$S_2(CH_2{\cdot}CH_2{\cdot}CO_2Et)_2$	15·88	16·01	16·34

If the constants for H (Part IX, *loc. cit.*) are subtracted from those found for SH, the following values for S (in thiols) are obtained:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
S (in thiols)	50·7	7·665	7·729	7·876	8·017	52·76

It will be noted that, apart from the molecular refraction coefficient, they differ from the constants for S deduced from dialkyl sulphides. Whether the constants for H in SH are identical with those for H in CH_2 must be regarded as a very open question and would serve to emphasise the great danger attending any attempt to assign constants for S independently of its mode of combination as Sugden has done for the parachor [compare oxygen where the constants for O (ethers), O (acetals), O (carbonyl), and O (hydroxyl) all differ].

Experimental.

Commercial Alkyl Thiols.—25—50 G. samples of the following thiols, supplied by Eastman Kodak, were carefully fractionated, and middle fractions collected for the physical measurements. Ethyl, b. p. 35·0°/768 mm. *n*-Propyl, b. p. 67·3°/755 mm. *iso*Propyl, b. p. 50·5°/753 mm. *n*-Butyl, b. p. 98°/765·5 mm. *iso*Butyl, b. p. 88°/764 mm. *tert.*-Butyl, b. p. 64°/749 mm. *n*-Amyl, b. p. 125°/771 mm. *iso*Amyl, b. p. 118·2—118·7°/765 mm. Thiophenol, b. p. 168°/758 mm.

n-*Hexylthiol.* The following modification of the method of Backer, Terpstra, and Dijkstra (*Rec. Trav. chim.*, 1932, **51**, 1166; compare *Org. Synth.*, 1941, **21**, 36) was employed. In a 500-ml. three-necked flask, equipped with a glycerol-sealed stirrer and a reflux condenser, was placed a mixture of 62·5 g. of *n*-hexyl bromide and a solution of 38 g. of thiourea in 25 ml. of water; the top of the condenser was connected by means of a glass tube to an inverted funnel just dipping into potassium permanganate solution. The mixture was refluxed with vigorous stirring for 2 hours: it became homogeneous after 30 minutes. A solution of 30 g. of sodium hydroxide in 30 ml. of water was added and the reaction mixture was refluxed with vigorous stirring for a further 2 hours. After cooling, the upper layer of crude thiol (35 g.) was separated: the aqueous layer was treated with a solution of 7 ml. of concentrated sulphuric acid in 50 ml. of water, extracted with ether, the extract combined with the crude thiol, dried ($CaSO_4$) and the solvent removed. Distillation yielded pure *n*-hexylthiol, b. p. 152·5°/762 mm.

n-*Heptylthiol.* This was prepared as for the the *n*-hexyl compound from 62 g. of *n*-heptyl iodide and a solution of 26·2 g. of thiourea in 16 ml. of hot water. The yield of crude thiol, b. p. 173—175°, was 38 g.: redistillation gave the pure thiol, b. p. 174°/766 mm.

n-*Octylthiol.* A highly purified sample was kindly supplied by the Connecticut Hard Rubber Co. and was fractionally distilled; b. p. 195°/761 mm.

Sulphur Monochloride.—Commercial "redistilled" sulphur monochloride was first redistilled from pure powdered sulphur and then fractionated in an all-glass apparatus; b. p. 135°/748 mm.

Phenyl Methyl Sulphide.—To a solution of 10 g. of sodium hydroxide in 100 ml. of water contained in a 500-ml. three-necked flask, equipped with a dropping funnel, mechanical stirrer, and reflux condenser, were added 27·5 g. of thiophenol during 30 minutes and the vigorous stirring was continued for a further 30 minutes. 31·6 G. of methyl sulphate were introduced during 1 hour and the mixture was refluxed, with constant stirring, for 7 hours. The sulphide layer was separated, washed thrice with 10% sodium hydroxide solution and then with water until the washings were neutral to litmus, dried, and distilled. The yield of phenyl methyl sulphide, b. p. 192—192·5°/761 mm., was 24 g.

Phenyl Ethyl Sulphide.—This was prepared exactly as detailed for the methyl compound except that 38·5 g. of ethyl sulphate replaced the methyl sulphate. The yield of phenyl ethyl sulphide, b. p. 204·5°/760 mm., was 32 g. This was redistilled under reduced pressure for the physical measurements; b. p. 69°/6 mm.

Phenyl n-*Propyl Sulphide.*—To a solution of sodium ethoxide, prepared from 5·75 g. of sodium and 150 ml. of absolute ethyl alcohol, were added 27·5 g. of thiophenol, followed by 64 g. of *n*-propyl iodide during 1 hour. The mixture was refluxed for 4 hours and then most of the alcohol was distilled off; the residue in the flask was diluted with water, the crude sulphide extracted with ether, the ethereal extract washed successively with 10% sodium hydroxide solution, water, dilute sulphuric acid and water, dried ($CaCl_2$), the solvent removed, and the residue distilled under reduced pressure. The yield of phenyl *n*-propyl sulphide, b. p. 74·5°/3·0 mm., was 25 g. In this and subsequent preparations, it is probably better to use the equivalent quantity of the alkyl halide.

Phenyl iso*Propyl Sulphide.*—This was prepared as for the *n*-propyl compound with the substitution of the *n*-propyl iodide by 64 g. of *iso*propyl iodide and the mixture was refluxed for 5 hours. The yield of sulphide, b. p. 70°/4 mm., was 32 g.

Phenyl n-*Butyl Sulphide.*—This was prepared as detailed for *n*-propyl sulphide with the substitution of 62 g. of *n*-butyl iodide for the *n*-propyl iodide. The yield of phenyl *n*-butyl sulphide, b. p. 104°/6 mm., was 34 g.

Phenyl n-*Amyl Sulphide.*—This sulphide was prepared from 5·75 g. of sodium in 150 ml. of absolute ethyl alcohol, 27·5 g. of thiophenol, and 74 g. of *n*-amyl iodide; the mixture was refluxed for 7 hours, and the compound isolated as above. The yield of *phenyl* n-*amyl sulphide*, b. p. 111·5°/5 mm., was 31 g. (Found: S, 17·8. $C_{11}H_{16}S$ requires S, 17·8%).

Phenyl n-*Hexyl Sulphide.*—To a solution of 5·25 g. of sodium in 150 ml. of absolute alcohol were added successively 25 g. of thiophenol and 37 g. of *n*-hexyl bromide. The mixture was refluxed for 6 hours and the *phenyl* n-*hexyl sulphide*, b. p. 124·5°/2·0 mm. (36 g.), isolated as usual (Found: S, 16·7. $C_{12}H_{18}S$ requires S, 16·5%).

483. *Ethylthiol.* B. p. 35·0°/768 mm.; *M* 62·13; n_C 1·42875, n_D 1·43168, n_F 1·43900, $n_{G'}$ 1·44465; R_C 18·91, R_D 19·02, R_F 19·30, $R_{G'}$ 19·52; $Mn_D^{20°}$ 88·95. Densities determined: $d_4^{20°}$ 0·8468, $d_4^{7·4°}$ 0·8536. Apparatus A = *. Apparatus *B* = **.

(These headings apply to all the following tables in this paper.)

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
9·4°	15·22	0·8525	24·30	162·0*	16·5°	12·00	0·8487	23·88	162·1**
17·2	14·85	0·8484	23·59	161·7*				Mean	161·9

484. n-*Propylthiol.* B. p. 67·3°/755 mm.; *M* 76·15; n_C 1·43333, n_D 1·43610, n_F 1·44302, $n_{G'}$ 1·44830; R_C 23·58, R_D 23·71, R_F 24·04, $R_{G'}$ 24·29; $Mn_D^{20°}$ 109·36. Densities determined: $d_4^{20°}$ 0·8398, $d_4^{40·9°}$ 0·8181. Apparatus *C*.

18·4°	12·56	0·8415	25·09	202·6	40·8°	11·43	0·8182	22·20	202·3
23·5	12·25	0·8362	24·32	202·4				Mean	202·4

485. iso*Propylthiol.* B. p. 50·6°/753 mm.; *M* 76·15; n_C 1·41618, n_D 1·41886, n_F 1·42551, $n_{G'}$ 1·43057; R_C 23·37, R_D 23·50, R_F 23·82, $R_{G'}$ 24·07; $Mn_D^{20°}$ 108·05. Densities determined: $d_4^{20°}$ 0·8182, $d_4^{44·2°}$ 0·7899. Apparatus *B*.

17·1°	11·55	0·8216	22·25	201·5	40·1°	10·49	0·7947	19·55	202·0
								Mean	201·8

486. n-*Butylthiol.* B. p. 98·1°/765·5 mm.; *M* 90·18; n_C 1·43977, n_D 1·44255, n_F 1·44932, $n_{G'}$ 1·45457; R_C 28·23, R_D 28·38, R_F 28·75, $R_{G'}$ 29·05; $Mn_D^{20°}$ 130·09. Densities determined: $d_4^{20°}$ 0·8417, $d_4^{40·9°}$ 0·8218, $d_4^{59·7°}$ 0·8036. Apparatus *A*.

21·9°	16·28	0·8399	25·57	241·5	60·9°	14·03	0·8025	21·08	241·1
41·2	15·22	0·8215	23·41	241·6				Mean	241·4

487. iso*Butylthiol.* B. p. 88°/764 mm.; *M* 90·18; n_C 1·43547, n_D 1·43822, n_F 1·44491, $n_{G'}$ 1·45011; R_C 28·22, R_D 28·38, R_F 28·75, $R_{G'}$ 29·04; $Mn_D^{20°}$ 129·70. Densities determined: $d_D^{20°}$ 0·8346, $d_4^{41·7°}$ 0·8126, $d_4^{62·9°}$ 0·7916. Apparatus *B*.

16·4°	12·36	0·8382	24·29	239·0	62·1°	10·53	0·7924	19·57	239·7
41·5	11·56	0·8128	22·03	240·4				Mean	239·7

488. tert.-*Butylthiol.* B. p. 64°/749 mm.; *M* 90·18; n_C 1·41973, n_D 1·42246, n_F 1·42918, $n_{G'}$ 1·43419; R_C 28·56, R_D 28·73, R_F 29·13, $R_{G'}$ 29·43; $Mn_D^{20°}$ 128·28. Densities determined: $d_4^{20°}$ 0·7985, $d_4^{40·8°}$ 0·7774. Apparatus *B*.

18·4°	11·03	0·8001	20·69	240·4	40·9°	10·01	0·7774	18·25	240·2
								Mean	240·3

489. n-*Amylthiol.* B. p. 125°/771 mm.; *M* 104·21; n_C 1·44385, n_D 1·44656, n_F 1·45328, $n_{G'}$ 1·45846; R_C 32·83, R_D 33·00, R_F 33·42, $R_{G'}$ 33·76; $Mn_D^{20°}$ 150·75. Densities determined: $d_4^{20°}$ 0·8431, $d_4^{41·1°}$ 0·8229, $d_4^{61·2°}$ 0·8053, $d_4^{85·5°}$ 0·7826. Apparatus *A*.

10·9°	17·10	0·8515	27·26	279·7	61·7°	14·76	0·8048	22·24	281·2
41·1	15·74	0·8229	24·25	281·0	87·3	13·54	0·7809	19·80	281·5
								Mean	281·1

490. iso*Amylthiol.* B. p. 118·2—118·7°/765 mm.; *M* 104·25; n_C 1·44096, n_D 1·44365, n_F 1·45022, $n_{G'}$ 1·45529; R_C 32·78, R_D 32·96, R_F 33·37, $R_{G'}$ 33·70; $Mn_D^{20°}$ 150·51. Densities determined: $d_4^{20°}$ 0·8398, $d_4^{40·8°}$ 0·8211, $d_4^{60·1°}$ 0·8035, $d_4^{85·7°}$ 0·7799. Apparatus *C*.

19·7°	12·76	0·8401	25·45	278·7	66·5°	11·21	0·7977	21·23	280·3
41·1	12·12	0·8208	23·62	280·0	89·4	10·00	0·7765	18·43	278·7
								Mean	279·4

491. n-*Hexylthiol.* B. p. 152·5°/762 mm.; M 118·23; n_C 1·44659, n_D 1·44937, n_F 1·45599, $n_{G'}$ 1·46074; R_C 37·41, R_D 37·61, R_F 38·09, $R_{G'}$ 38·43; $Mn_D^{20°}$ 171·36. Densities determined: $d_{4°}^{20°}$ 0·8438, $d_{4°}^{40·2°}$ 0·8268, $d_{4°}^{59·5°}$ 0·8109, $d_{4°}^{86·7°}$ 0·7874. Apparatus *E*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
14·3°	14·22	0·8485	28·10	320·8	61·2°	12·43	0·8095	23·43	321·3
16·9	14·13	0·8464	27·85	320·9	87·4	11·50	0·7868	21·07	322·0
40·8	13·19	0·8263	25·38	321·2				Mean	321·2

492. n-*Heptylthiol.* B. p. 174°/766 mm.; M 132·26; n_C 1·44766, n_D 1·45207, n_F 1·45672, $n_{G'}$ 1·46128; R_C 42·04, R_D 42·25, R_F 42·77, $R_{G'}$ 43·14; $Mn_D^{20°}$ 191·82. Densities determined: $d_{4°}^{20°}$ 0·8417, $d_{4°}^{40·2°}$ 0·8260, $d_{4°}^{62·1°}$ 0·8087, $d_{4°}^{85·5°}$ 0·7900. Apparatus *E*.

16·0°	14·16	0·8449	27·86	359·7	61·3°	12·57	0·8093	23·69	359·7
40·9	13·08	0·8254	25·14	358·8	86·7	11·84	0·7891	21·76	362·0
								Mean	359·9

Consistent results for the surface tensions can only be obtained if the compound is freshly redistilled.

493. n-*Octylthiol.* B. p. 195°/761 mm.; M 146·28; n_C 1·45112, n_D 1·45377, n_F 1·46021, $n_{G'}$ 1·46498; R_C 46·74, R_D 46·98, R_F 47·55, $R_{G'}$ 47·98; $Mn_D^{20°}$ 212·66. Densities determined: $d_{4°}^{20°}$ 0·8429, $d_{4°}^{40·0°}$ 0·8282, $d_{4°}^{61·4°}$ 0·8120, $d_{4°}^{85·9°}$ 0·7930. Apparatus *E*.

19·2°	14·18	0·8435	27·86	398·4	61·1°	12·89	0·8122	24·38	400·1
40·8	13·52	0·8276	26·06	399·4	86·5	12·12	0·7925	22·37	401·4
								Mean	399·8

494. *Thiophenol.* B. p. 168°/758 mm.; M 110·18; n_C 1·58325, n_D 1·58973, n_F 1·61201, $n_{G'}$ very faint; R_C 34·22, R_D 34·52, R_F 35·57; $Mn_D^{20°}$ 175·15. Densities determined: $d_{4°}^{20°}$ 1·0766, $d_{4°}^{40·6°}$ 1·0583, $d_{4°}^{59·8°}$ 1·0406, $d_{4°}^{85·7°}$ 1·0168. Apparatus *A*.

18·9°	19·46	1·0776	39·27	256·0	41·1°	18·39	1·0577	36·42	255·9
25·3	19·07	1·0718	38·27	255·7	64·8	17·34	1·0361	33·64	256·1
								Mean	255·9

495. *Phenyl methyl sulphide.* B. p. 192—192·5°/761 mm.; M 124·19; n_C 1·58101, n_D 1·58747, n_F 1·60443, $n_{G'}$ 1·61871 (line faint); R_C 39·09, R_D 39·42, R_F 40·34, $R_{G'}$ 41·11; $Mn_D^{20°}$ 197·15. Densities determined: $d_{4°}^{20°}$ 1·0594, $d_{4°}^{42·3°}$ 1·0397, $d_{4°}^{61·3°}$ 1·0215, $d_{4°}^{85·9°}$ 0·9996. Apparatus *A*.

20·4°	20·33	1·0590	40·31	295·5	60·3°	18·44	1·0224	35·30	296·0
41·4	19·33	1·0405	37·66	295·7	86·4	17·18	0·9991	32·14	296·0
								Mean	295·6

496. *Phenyl ethyl sulphide.* B. p. 204·5°/759 mm.; M 138·22; n_C 1·56070, n_D 1·56656, n_F 1·58115, $n_{G'}$ 1·59442 (line faint); R_C 43·81, R_D 44·19, R_F 45·12, $R_{G'}$ 45·95; $Mn_D^{20°}$ 216·54. Densities determined: $d_{4°}^{20°}$ 1·0211, $d_{4°}^{40·2°}$ 1·0028, $d_{4°}^{60·4°}$ 0·9858, $d_{4°}^{87·3°}$ 0·9614. Apparatus *B*.

22·5°	15·44	1·0189	36·89	334·3	60·2°	14·01	0·9860	32·39	334·4
40·5	14·72	1·0025	34·60	334·4	86·9	13·11	0·9618	29·57	335·3
								Mean	334·4

497. *Phenyl* n-*propyl sulphide.* B. p. 74·5°/3·0 mm.; M 152·25; n_C 1·54978, n_D 1·55521, n_F 1·56938, $n_{G'}$ 1·58115; R_C 48·46, R_D 48·85, R_F 49·88, $R_{G'}$ 50·72; $Mn_D^{20°}$ 236·78. Densities determined: $d_{4°}^{20°}$ 1·0006, $d_{4°}^{40·4°}$ 0·9830, $d_{4°}^{60·2°}$ 0·9671, $d_{4°}^{85·6°}$ 0·9458. Apparatus *D*.

19·9°	14·31	1·0007	35·36	371·0	61·1°	12·98	0·9663	30·98	371·7
26·3	14·17	0·9953	34·83	371·6	86·4	12·21	0·9451	28·50	372·2
40·6	13·65	0·9828	33·13	371·7				Mean	371·6

498. *Phenyl* iso*propyl sulphide.* B. p. 70°/4 mm.; M 152·25; n_C 1·54114, n_D 1·54641, n_F 1·56006, $n_{G'}$ 1·57135; R_C 48·59, R_D 48·98, R_F 50·00, $R_{G'}$ 50·82; $Mn_D^{20°}$ 235·44. Densities determined: $d_{4°}^{20°}$ 0·9848, $d_{4°}^{40·6°}$ 0·9677, $d_{4°}^{61·4°}$ 0·9505, $d_{4°}^{85·7°}$ 0·9298. Apparatus *D*.

17·4°	13·89	0·9870	33·86	372·1	60·7°	12·42	0·9511	29·17	372·0
23·9	13·60	0·9815	32·97	372·0	86·5	11·55	0·9291	26·50	371·8
41·1	13·03	0·9673	31·13	371·8				Mean	371·9

499. *Phenyl* n-*butyl sulphide.* B. p. 104°/6 mm.; M 162·27; n_C 1·54145, n_D 1·54658, n_F 1·55994, $n_{G'}$ 1·57102; R_C 53·18, R_D 53·59, R_F 54·68, $R_{G'}$ 55·57; $Mn_D^{20°}$ 257·14. Densities determined: $d_{4°}^{20°}$ 0·9831, $d_{4°}^{40·5°}$ 0·9674, $d_{4°}^{62·1°}$ 0·9500, $d_{4°}^{86·6°}$ 0·9304. Apparatus *D*.

18·4°	14·26	0·9843	34·67	409·9	61·3°	12·98	0·9506	30·47	411·0
24·3	14·12	0·9797	34·16	410·3	86·5	12·20	0·9305	28·04	411·2
41·0	13·53	0·9670	32·31	409·9				Mean	410·5

500. *Phenyl* n-*amyl sulphide.* B. p. 111·5°/5 mm.; *M* 180·30; n_C 1·53498, n_D 1·53990, n_F 1·55263, $n_{G'}$ 1·56300; R_C 57·79, R_D 58·23, R_F 59·37, $R_{G'}$ 60·29; $Mn_D^{20°}$ 277·64. Densities determined: $d_{4°}^{20°}$ 0·9713, $d_{4°}^{40·8°}$ 0·9557, $d_{4°}^{60·8°}$ 0·9408, $d_{4°}^{86·2°}$ 0·9207. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
17·6°	18·82	0·9731	34·29	448·4	61·2°	17·14	0·9405	30·20	449·4
25·9	18·68	0·9668	33·82	449·7	86·6	16·17	0·9204	27·87	450·1
41·6	17·87	0·9551	31·96	448·8				Mean	449·3

501. *Phenyl* n-*hexyl sulphide.* B. p. 124·5°/2·0 mm.; *M* 194·32; n_C 1·52894, n_D 1·53358, n_F 1·54577, $n_{G'}$ 1·55552; R_C 62·50, R_D 62·96, R_F 64·16, $R_{G'}$ 65·10; $Mn_D^{20°}$ 298·01. Densities determined: $d_{4°}^{20°}$ 0·9588, $d_{4°}^{41·0°}$ 0·9432, $d_{4°}^{60·2°}$ 0·9287, $d_{4°}^{86·0°}$ 0·9094. Apparatus *D*.

22·1°	18·55	0·9572	43·85	522·4	58·3°	17·22	0·9301	39·55	523·9
26·9	18·33	0·9536	43·17	522·3	85·1	16·12	0·9101	36·23	523·8
40·7	17·86	0·9434	41·61	523·1				Mean	523·1

502. *Sulphur monochloride.* B. p. 135°/748 mm.; *M* 135·04; n_D 1·6500; R_D 29·36; $Mn_D^{20°}$ 222·82. Densities determined: $d_{4°}^{20°}$ 1·6776, $d_{4°}^{40·5°}$ 1·6467, $d_{4°}^{60·6°}$ 1·6157, $d_{4°}^{85·7°}$ 1·5778. Apparatus *C*.

16·3°	10·98	1·6832	43·88	206·5	85·1°	9·04	1·5787	33·88	206·4
62·0	9·66	1·6136	37·00	206·4				Mean	206·4

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368. *Physical Properties and Chemical Constitution. Part XXII. Some Primary, Secondary, and Tertiary Amines.*

By ARTHUR I. VOGEL.

New determinations have been made of the refractivities at 20° and the parachors of a series of primary aliphatic amines, secondary aliphatic and aromatic amines, and tertiary aliphatic and aromatic amines. By combining the new data with the constants for the alkyl groups (Part XI, this vol., p. 611) and for phenyl (Part XV, this vol., p. 654), the following new constants have been evaluated:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
NH_2 (primary aliphatic amine).....	44·0	4·414	4·438	4·507	4·570	22·64
NH (secondary aliphatic amine) ...	28·4	3·572	3·610	3·667	3·732	23·34
NH (secondary aromatic amine) ...	27·1	4·548	4·678	5·000	5·273	29·52
N (tertiary aliphatic amine).....	7·2	2·698	2·744	2·820	2·914	24·37
N (tertiary aromatic amine).....	?	4·085	4·243	4·675	5·155	30·23

The corresponding values for N in primary and secondary amines, deduced by subtracting the constants for H in CH_3 (Part IX, *J.*, 1946, 133), are:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
N (primary aliphatic amine).....	12·6	2·356	2·376	2·414	2·482	27·80
N (secondary aliphatic amine).....	12·7	2·546	2·582	2·624	2·692	25·90
N (secondary aromatic amine).....	11·4	3·522	3·550	3·957	4·223	32·08

THE different contributions of nitrogen to the molecular refractivity according to the state of combination have long been recognised. For instance, Brühl (for review, see Eisenlohr, "Spektrochemie organischer Verbindungen: Molekularrefraktion und -dispersion", Ferdinand Enke, 1912, pp. 55, 62) has computed values for nitrogen in primary, secondary, and tertiary aliphatic and aromatic amines as well as in many other states of combination. Eisenlohr (in Landolt–Börnstein, "Tabellen", 1923, II, 985) gives the following constants for nitrogen:

	R_C.	R_D.	R_F.	$R_{G'}$.
N (in primary amines)	2·309	2·322	2·368	2·397
N (in secondary amines)	2·478	2·502	2·561	2·605
N (in tertiary amines)	2·808	2·840	2·940	3·000
N (in tertiary imides)	3·740	3·776	3·877	3·962
N (in cyanides)	3·102	3·118	3·155	3·173

In the original table of atomic and structural parachors, Sugden (*J.*, 1924, **125**, 1180) gave "N = (12·5)" and stated (*loc. cit.*, p. 1179): "Certain figures which are deduced from one or two compounds only, or which are based on somewhat doubtful data, are enclosed in brackets and can only be regarded as provisional values". The data from which this value was deduced are not stated, but this "provisional value" was widely employed in various tables in that paper.

Presumably the figure 12·5 was subsequently adopted but no additional evidence seems to have been published (see, *e.g.*, Sugden, Reed, and Wilkins, *J.*, 1925, **127**, 1526; Henley and Sugden, *J.*, 1929, 1060; Sugden, " The Parachor and Valency ", 1930, p. 38).

New determinations of the refractivities at 20° and the parachors of a series of primary alkylamines have now been made, and the NH_2 contributions computed by subtraction of the constants for alkyl groups (Part XI, *loc. cit.*). Only one polymethylene diamine (ethylenediamine) has so far been investigated: this, coupled with the constants for CH_2 (Part IX, *J.*, 1946, 133), provides an independent determination of the NH_2 constants. All the results are collected in Table I, and the mean values have been deduced from all the alkylamines except *sec.*-butylamine.

TABLE I.

Values for NH_2 *from primary amines.*

Amine.	*P.*	R_C.	R_D.	R_F.	$R_{C'}$.	$Mn_D^{20°}$.
NH_2Pr^n	44·1	4·46	4·48	4·56	4·61	22·81
NH_2Bu^n	43·3	4·35	4·37	4·44	4·49	22·65
NH_2Bu^i	42·8	4·34	4·36	4·42	4·56	22·64
NH_2Bu^s *	46·9	4·66	4·68	4·75	4·81	21·69
NH_2Am^n	44·5	4·44	4·47	4·53	4·58	22·56
NH_2Am^i	44·4	4·41	4·44	4·52	4·56	22·54
$NH_2 \cdot C_6H_{13}^n$	44·4	4·41	4·43	4·51	4·56	22·39
$NH_2 \cdot C_7H_{15}^n$	—	4·39	4·41	4·47	4·53	22·38
$NH_2 \cdot C_8H_{17}^n$	—	4·47	4·49	4·57	4·64	22·28
$NH_2 \cdot C_2H_5$	43·2	4·43	4·46	4·52	4·58	23·51
$NH_2 \cdot CH_2 \cdot CH_2 \cdot NH_2$	45·5	4·44	4·47	4·53	4·59	22·68
Mean NH_2 (excluding *)	44·0	4·414	4·438	4·507	4·570	22·64
$C_6H_5 \cdot NH_2$	41·8	5·13	5·20	5·40	—	25·63
$C_6H_5 \cdot CH_2 \cdot NH_2$	45·1	4·26	4·26	4·32	4·34	21·05
$C_6H_{11} \cdot NH_2$	47·1	4·63	4·68	4·75	4·80	21·70

The figures deduced from aniline and benzylamine are given at the end of the table for purposes of comparison: the constants for phenyl were those from Part XV (this vol., p. 654) and for benzyl from $C_6H_5 \cdot CH_2Cl$ − Cl (XIV, **281**). The constants from *cyclo*hexylamine, $C_6H_{11} \cdot NH_2$, deduced with the aid of the data for di*cyclo*hexyl (XIX, **445**), are not regarded as very trustworthy in view of the difficulties attending the manipulation of this strongly fuming compound.

The constants for the secondary amine group, >NH, have been deduced by two independent methods: (1) From dialkylamines and alkyl groups in aliphatic hydrocarbons: under this heading must be included di*cyclo*hexylamine, *i.e.*, $C_6H_{11} \cdot NH \cdot C_6H_{11}$ − $C_6H_{11} \cdot C_6H_{11}$ (XIX, **445**). (2) From ethyl *N*-alkylcarbamates and esters, *e.g.*, $CH_3 \cdot NH \cdot CO_2C_2H_5$ − $CH_3 \cdot CO_2C_2H_5$ (XIII, **189**). It will be noted that the constants for CH_2 are not involved. The results are summarised in Table II; in the calculation of the mean values, the figures for secondary aliphatic amines containing secondary alkyl groups have been omitted. The values for NH computed from secondary aromatic amines $C_6H_5 \cdot NHAlkyl$ − $C_6H_5 \cdot Alkyl$ (Part X, this vol., p. 607) are given in Table III; the parachor contribution agrees within about 1 unit, but the refractivities are uniformly higher. The measurements of $n_{C'}$ for secondary aromatic amines with a Pulfrich refractometer are difficult because of the faintness of the line and in consequence the values for $R_{C'}$ for these compounds are somewhat less trustworthy.

TABLE II.

Values for NH *from secondary aliphatic amines.*

	P.	R_C.	R_D.	R_F.	$R_{C'}$.	$Mn_D^{20°}$.
$NHEt_2$	29·5	3·66	3·70	3·77	3·86	23·96
$NHPr_2^n$	28·0	3·57	3·62	3·66	3·72	23·68
$NHPr_2^i$	29·0	3·67	3·69	3·75	5·84	24·00
$NHBu_2^n$	28·2	3·61	3·65	3·70	3·78	23·61
$NHBu_2^i$	28·1	3·57	3·59	3·66	3·72	23·03
$NHBu_2^s$ *	31·7	3·73	3·74	3·81	3·88	21·92
$NHAm_2^n$	28·7	3·46	3·49	3·55	3·61	23·57
$NHAm_2^i$	28·4	3·58	3·63	3·69	3·74	23·30
$C_6H_{11} \cdot NH \cdot C_6H_{11}$	30·4	3·66	3·69	3·76	3·81	23·11
$CH_3 \cdot NH \cdot CO_2C_2H_5$	27·6	3·44	3·49	3·55	3·60	25·44 *
$CH_3 \cdot CH_2 \cdot NH \cdot CO_2C_2H_5$	27·0	3·60	3·63	3·69	3·75	25·19 *
Mean NH (excluding *)	28·4	3·572	3·610	3·667	3·732	23·34

TABLE III.

Values for NH *from secondary aromatic amines.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
NHMePh	27·9	4·46	4·57	4·90	5·19	30·43
NHEtPh	27·2	4·56	4·70	5·02	5·24	29·50
NHPr^{n}Ph	26·2	4·57	4·72	5·03	5·32	29·22
NHBu^{n}Ph	27·0	4·60	4·72	5·05	5·34	28·91
Mean NH	27·1	4·548	4·678	5·000	5·273	29·52

New determinations have also been made of the refractivities at 20° and the parachors of a number of tertiary amines. The data for trialkylamines have been employed in the evaluation in the usual manner of the contributions of the N atom. The results are presented in Table IV :

TABLE IV.

Values for N *from tertiary aliphatic amines.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	Mn_D^{20}.
NEt_3	10·6	2·84	2·89	2·99	3·10	28·61
NPr^n_3	6·7	2·75	2·78	2·87	2·98	25·29
NBu^n_3	6·0	2·70	2·74	2·82	2·90	25·57
NAm^n_3	6·4	2·52	2·57	2·61	2·70	25·36
NAm^i_3	6·4	2·68	2·74	2·81	2·89	25·02
Mean N	7·2	2·698	2·744	2·820	2·914	24·37
$C_6H_5{\cdot}CH_2{\cdot}NEt_2$	7·0	2·65	2·68	2·76	2·86	22·59

the values deduced from benzyldiethylamine are also included (the constants for the benzyl group were computed from $C_6H_5{\cdot}CH_2Cl - Cl$) and are in moderate agreement with the mean constants. For tertiary aromatic amines, $NPhAlk_2$, the constants for N have been computed by subtracting {Ph (Part XV, *loc. cit.*) + 2Alkyl (Part XI, *loc. cit.*)}. All the results are collected in Table V. It will be noted that the parachor for N appears to decrease as the molecular weight of the alkyl group increases; it is hoped to confirm the surface-tension results by the method of maximum bubble pressure in order to rule out the possibility that the decreasing parachor values are due to slight departures from zero contact angles.

TABLE V.

Values for N *from tertiary aromatic amines.*

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
NMe_2Ph	11·5	3·99	4·15	4·50	4·95	29·48
NEt_2Ph	7·9	4·08	4·24	4·68	5·20	30·61
NPr^n_2Ph	3·8	4·12	4·27	4·73	5·22	30·49
NBu^n_2Ph	2·3	4·15	4·31	4·79	5·25	30·32
Mean N	?	4·085	4·243	4·675	5·155	30·23

The results deduced from ethyl nitrilotricarboxylate, $N(CO_2Et)_3$, are of interest. If the CO_2Et constants are calculated from ethyl oxalate (XIII, **236**), the following values for N are obtained : P 13·2; R_C 2·41; R_D 2·44; R_F 2·48; $R_{G'}$ 2·51; $Mn_D^{20°}$ 24·12. The use of the mean constants for COO (esters), deduced in Part XIII (this vol., p. 624), leads to abnormal results.

It is instructive to calculate the constants for N by subtracting the values for H in CH_2 (Part IX, *J.*, 1946, 133) from the mean values for NH_2 and NH. The results are given below.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
N (in primary aliphatic amines) ...	12·6	2·362	2·382	2·421	2·490	27·76
N (in secondary aliphatic amines) ...	12·7	2·546	2·582	2·624	2·692	25·90
N (in secondary aromatic amines) ...	11·4	3·522	3·550	3·957	4·233	32·08
N (in cyanides)	15·4	0·900	0·891	0·851	0·822	23·31

The following conclusions may be drawn from these figures : (1) The parachor for N is approximately the same in primary and in secondary amines but differs from that in tertiary amines (compare Sugden who gives, and uses, one value for N in all nitrogen compounds). (2) The refractivities for N differ according to the state of combination * and at least five values for N in amines (primary aliphatic; secondary aliphatic; secondary aromatic; tertiary aliphatic; and tertiary aromatic) are necessary. This view would agree with that originally expressed by

* A sufficient number of primary aromatic amines has not yet been investigated by the author to decide whether N in these differsf rom that in primary aliphatic amines.

Brühl but differs from that of Eisenlohr; the refractivities deduced by Eisenlohr (compare *Z. physikal. Chem.*, 1912, **79**, 129; Landolt–Börnstein, " Tabellen ", 1923, II, 985) for N in primary, secondary, and tertiary amines, which are widely quoted (see, *e.g.*, Ostwald–Luther, " Hilfsbuch zur Ausführung physiko-chemischer Messungen ", Akad. Verlag, 5th Edition, 1931, p. 910; Fajans, in Weissberger, " Physical Methods of Organic Chemistry ", Interscience, 1945, I, 673), are consequently meaningless and definitely misleading. The constants for N in cyanides have been computed from CN − (C + ⋿, terminal) (Part XVII, this vol., p. 674).

The question of the refraction of the various electron groups involving nitrogen will form the subject of a future communication (compare Smyth, " Dielectric Constant and Molecular Structure ", Chemical Catalog Co., 1931, p. 152; Denbigh, *Trans. Faraday Soc.*, 1940, **36**, 397).

Experimental.

Primary aliphatic amines. 25—50 G. samples of the pure commercial products were dried over potassium hydroxide pellets and fractionated, with adequate precautions against the entrance of moisture, in an all-glass apparatus, and three middle fractions were collected for the physical measurements. The purified specimens were kept in Pyrex test-tubes, closed with corks covered with tin or platinum foil, and used immediately after distillation. Precautions were taken as far as possible to prevent the entrance of moisture during the measurements. The b. p.s are given under the physical measurements below. The sources of the various amines were as follows:—*n*-propyl, allyl, *n*-butyl, *iso*butyl, *sec.*-butyl, *n*-amyl, and *iso*amyl, from Eastman Kodak; *n*-hexyl, *n*-heptyl, and *n*-octyl from Sharples; *cyclo*hexyl from Light; ethylenediamine from Eastman Kodak.

Aniline. A.R. Aniline (Hopkin and Williams) was dried with potassium hydroxide pellets and distilled from an all-glass apparatus; b. p. 184·5°/750 mm.

Benzylamine. A pure B.D.H. sample was dried over potassium hydroxide pellets and twice distilled from an all-glass apparatus; b. p. 185°/767 mm.

Secondary aliphatic amines. The pure commercial products were purified and manipulated as detailed for primary aliphatic amines. Diethylamine and di-*n*-butylamine were presented by Sharples; di-*n*-propyl-, di*iso*propyl-, di*iso*butyl-, di-*sec.*-butyl-, di-*n*-amyl-, and di*iso*amyl-amine were purchased from Eastman Kodak.

*Di*cyclo*hexylamine.* The commercial product (Light) was distilled, and the fraction, b. p. 251·5°/760 mm., collected; this had a very pale green colour, which was removed upon distillation under reduced pressure; b. p. 113·5°/9 mm.

N-*Nitrosomethylaniline.* This was prepared from B.D.H. pure monomethylaniline according to *Org. Synth.*, 1933, **13**, 82, except that a 1-l. beaker replaced the 3-l. flask, the extraction with benzene was omitted, and the compound was dried with anhydrous calcium sulphate; the yield was not appreciably affected. The *N*-nitrosomethylaniline had b. p. 120°/13 mm. The b. p. of 135—137°/13 mm. recorded in *Organic Syntheses* would appear to be in error.

N-*Nitrosoethylaniline.* This was prepared similarly to the methyl compound from B.D.H. pure monoethylaniline; b. p. 131°/20 mm.

Monomethylaniline. 78 G. of pure *N*-nitrosomethylaniline were reduced with 150 g. of tin and 300 ml. of concentrated hydrochloric acid, affording 46 g. of pure, colourless monomethylaniline, b. p. 193°/738 mm.

Monoethylaniline. 75 G. of pure *N*-nitrosoethylaniline were similarly reduced and yielded 43 g. of pure, almost colourless monoethylaniline, b. p. 202·5°/750 mm.

Mono-n-*propylaniline.* 230 G. of A.R. aniline were heated with 123 g. of *n*-propyl bromide for 8 hours and the excess of aniline was removed by precipitation with 50% zinc chloride solution (Hickinbottom, *J.*, 1930, 993). The secondary amine was isolated by several extractions with light petroleum (b. p. 60—80°), the solvent removed, and the product fractionated. The crude amine (85 g.) distilled at 218—222°. Redistillation from a little zinc dust gave pure *n*-propylaniline, b. p. 219°/758 mm., $d_{4^\circ}^{20^\circ}$ 0·9460, $n_D^{20^\circ}$ 1·54375. For the physical measurements, the compound was distilled under reduced pressure; b. p. 96°/9 mm.

Mono-n-*butylaniline.* A commercially pure sample, kindly presented by Sharples Chemicals Inc., was fractionated from a little zinc dust, and the fraction, b. p. 237—238°/760 mm., collected. Redistillation gave a colourless product, b. p. 105°/3 mm.

Ethyl N-*methylcarbamate.* This was prepared from 33% aqueous methylamine solution, ethyl chloroformate, and sodium hydroxide solution, but the product was distilled under normal pressure and not under reduced pressure (cf. *Org. Synth.*, 1932, **12**, 38). The ester distilled as a colourless liquid, b. p. 169·5°/769 mm., and there was no sign of decomposition.

Ethyl N-*ethylcarbamate.* This compound was prepared from 110 ml. of ether, 90 g. of 33% aqueous ethylamine solution, 72·5 g. of ethyl chloroformate, and 26·5 g. of A.R. sodium hydroxide dissolved in 40 ml. of water (see *Org. Synth.*, 1932, **12**, 38). The yield of pure, colourless ester, b. p. 175°/748 mm., was 64 g.

Tertiary aliphatic amines. The pure commercial products (triethylamine, tri-*n*-butylamine, and benzyldiethylamine from Sharples; tri-*n*-propylamine, tri-*n*-amylamine, and tri*iso*amylamine from Eastman Kodak) were shaken mechanically with about half the volume of A.R. potassium hydroxide pellets, filtered, and distilled from sodium in a flask with a fractionating side arm, due precautions being taken to prevent access of moisture. The b. p.s are given under the physical properties.

Ethyl nitrilotricarboxylate. This was prepared from urethane, dry ether, sodium, and ethyl chloroformate (*Org. Synth.*, 1944, **24**, 60) and was twice distilled under reduced pressure; b. p. 143°/10 mm.

Dimethylaniline. A mixture of 50 g. of A.R. dimethylaniline and 25 g. of redistilled acetic anhydride was refluxed for 3 hours and then distilled until about 10 ml. remained; the residue contained any acetyl derivatives which might have been present (compare Brand and Franz, *J. pr. Chem.*, 1927, **115**,

153). The fraction, b. p. 193—194°, was collected separately and redistilled; pure dimethylaniline was collected at 194°/760 mm. (acetanilide has b. p. 305°/760 mm.; acetomethylanilide has b. p. 253°/712 mm.).

Diethylaniline. A mixture of 50 g. of redistilled diethylaniline, b. p. 214—215°, and 30 g. of redistilled acetic anhydride was refluxed for 4 hours, and the pure diethylaniline, b. p. 214·5°/748 mm., was isolated as for dimethylaniline. This was distilled under reduced pressure for the physical measurements; b. p. 86·5°/6 mm.

Di-n-*propylaniline.* A mixture of 45 g. of *n*-propylaniline, b. p. 218—220°/758 mm. (mainly 219°), and 82 g. of *n*-propyl bromide was refluxed for 9 hours. The solid reaction product was rendered alkaline with sodium hydroxide solution, and the upper layer separated. This was washed with water, dried ($MgSO_4$), and distilled: the excess of *n*-propyl bromide (35 g.) passed over at 72—73°, followed by the di-*n*-propylaniline (37 g.) at 241—243°/758 mm. (mainly 242°) as a very pale yellow liquid. The colour could be completely removed by distillation from a little zinc dust. For the physical measurements, the colourless product was redistilled under reduced pressure: b. p. 95°/4 mm.

Di-n-*butylaniline.* A mixture of 37 g. of *n*-butylaniline, b. p. 237—238°, and 68 g. of *n*-butyl bromide was heated on a boiling water-bath for 16 hours by which time the reaction product was solid. It was treated with sodium hydroxide solution until alkaline, and ether was added to facilitate separation of the organic layer. The ethereal extract was washed with water, dried, and the solvent removed: distillation yielded 22 g. of *n*-butyl bromide, b. p. 90—110°, and 37 g. of di-*n*-butylaniline, b. p. 269—270°/760 mm. The pale colour was removed by distillation under reduced pressure: b. p. 123°/6 mm.

503. n-*Propylamine.* B. p. 48°/750 mm.; *M* 59·11; n_C 1·38604, n_D 1·38815, n_F 1·39339, $n_{G'}$ 1·39715; R_C 19·36, R_D 19·45, R_F 19·69, $R_{G'}$ 19·85; $Mn_D^{20°}$ 82·06. Densities determined: $d_{4°}^{20°}$ 0·7173, $d_{4°}^{40·8°}$ 0·6955. Apparatus *A*.

(These headings apply to all subsequent tables in this paper.)

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
19·2°	16·52	0·7181	22·21	178·9	38·0°	15·51	0·6984	20·28	180·0
26·4	16·26	0·7106	21·64	179·7	41·6	15·18	0·6947	19·75	179·8
								Mean	179·6

504. n-*Butylamine.* B. p. 77°/750 mm.; *M* 73·14; n_C 1·39870, n_D 1·40086, n_F 1·40613, $n_{G'}$ 1·41003; R_C 23·85, R_D 23·96, R_F 24·24, $R_{G'}$ 24·44; $Mn_D^{20°}$ 102·46. Densities determined: $d_{4°}^{20°}$ 0·7414, $d_{4°}^{41·1°}$ 0·7222, $d_{4°}^{62·0°}$ 0·7020.

19·2°	13·11	0·7421	24·03	218·2	40·8°	12·16	0·7225	21·70	218·7
27·9	12·78	0·7341	23·17	218·6	61·7	11·12	0·7023	19·29	218·7
								Mean	218·6

505. iso*Butylamine.* B. p. 67·5°/753 mm.; *M* 73·14; n_C 1·39485, n_D 1·39700, n_F 1·40223, $n_{G'}$ 1·40601; R_C 23·87, R_D 23·98, R_F 24·26, $R_{G'}$ 24·46; $Mn_D^{20°}$ 102·18. Densities determined: $d_{4°}^{20°}$ 0·7346, $d_{4°}^{40·7°}$ 0·7143, $d_{4°}^{60·1°}$ 0·6952. Apparatus *D*.

19·7°	12·26	0·7349	22·25	216·3	41·4°	11·31	0·7136	19·93	216·9
24·5	12·14	0·7302	21·89	216·8	61·2	10·39	0·6941	17·81	217·1
25·5	12·06	0·7290	21·71	216·7				Mean	216·6

506. sec.-*Butylamine.* B. p. 63·5°/764 mm.; *M* 73·14; n_C 1·39107, n_D 1·39320, n_F 1·39843, $n_{G'}$ 1·40217; R_C 23·99, R_D 24·10, R_F 24·38, $R_{G'}$ 24·59; $Mn_D^{20°}$ 101·90. Densities determined: $d_{4°}^{20°}$ 0·7246, $d_{4°}^{41·0°}$ 0·7051. Apparatus *A*.

21·0°	15·86	0·7237	21·49	217·8	41·3°	14·67	0·7048	19·36	218·3
27·4	15·56	0·7177	20·91	218·2				Mean	218·1

507. n-*Amylamine.* B. p. 104·5°/761 mm.; *M* 87·16; n_C 1·40928, n_D 1·41147, n_F 1·41688, $n_{G'}$ 1·42070; R_C 28·58, R_D 28·72, R_F 29·05, $R_{G'}$ 29·28; $Mn_D^{20°}$ 123·02. Densities determined: $d_{4°}^{20°}$ 0·7544, $d_{4°}^{42·0°}$ 0·7343, $d_{4°}^{62·3°}$ 0·7170, $d_{4°}^{86·0°}$ 0·6966. Apparatus *D*.

20·1°	13·53	0·7543	25·20	258·9	63·5°	11·74	0·7159	20·76	260·2
22·4	13·45	0·7524	24·99	259·0	87·1	10·68	0·6956	18·35	260·0
42·1	12·62	0·7342	22·88	259·6				Mean	259·5

508. iso*Amylamine.* B. p. 96·5—97·5°/767 mm.; *M* 87·16; n_C 1·40611, n_D 1·40830, n_F 1·41366, $n_{G'}$ 1·41741; R_C 28·58, R_D 28·72, R_F 29·06, $R_{G'}$ 29·28; $Mn_D^{20°}$ 122·75. Densities determined: $d_{4°}^{20°}$ 0·7491, $d_{4°}^{40·9°}$ 0·7315, $d_{4°}^{61·4°}$ 0·7129, $d_{4°}^{86·8°}$ 0·6890. Apparatus *D*

25·3°	12·67	0·7445	23·30	257·2	62·0°	11·10	0·7122	19·52	257·6
29·4	12·48	0·7403	22·82	257·3	87·6	10·03	0·6883	17·05	257·9
43·1	11·97	0·7296	21·57	257·4				Mean	257·5

509. n-*Hexylamine.* B. p. 130°/762 mm.; *M* 101·19; n_C 1·41579, n_D 1·41801, n_F 1·42340, $n_{G'}$ 1·42750; R_C 33·14, R_D 33·29, R_F 33·67, $R_{G'}$ 33·95; $Mn_D^{20°}$ 143·49. Densities determined: $d_{4°}^{20°}$ 0·7660, $d_{4°}^{41·3°}$ 0·7481, $d_{4°}^{60·6°}$ 0·7322, $d_{4°}^{85·6°}$ 0·7106. Apparatus *C*.

13·0°	14·69	0·7719	26·92	298·6	60·6°	12·73	0·7322	22·13	299·7
40·5	13·64	0·7488	24·25	299·9	86·6	11·54	0·7098	19·45	299·4
								Mean	299·4

510. n-*Heptylamine.* B. p. 153·5°/762 mm.; *M* 115·22; n_C 1·42225, n_D 1·42451, n_F 1·42994, n_G 1·43398; R_C 37·79, R_D 37·96, R_F 38·38, $R_{G'}$ 38·70; $Mn_D^{20°}$ 164·13. Densities determined: $d_{4°}^{20°}$ 0·7754, $d_{4°}^{40·0°}$ 0·7601, $d_{4°}^{59·5°}$ 0·7443, $d_{4°}^{84·7°}$ 0·7244.

The compound does not wet glass and erratic results were obtained in the surface-tension measurements.

511. n-*Octylamine.* B. p. 176·5°/763 mm.; *M* 129·24; n_C 1·42694, n_D 1·42922, n_F 1·43471, $n_{G'}$ 1·43890; R_C 42·43, R_D 42·63, R_F 43·11, $R_{G'}$ 43·47; $Mn_D^{20°}$ 184·71. Density determined: $d_{4°}^{20°}$ 0·7819. The surface tension results were erratic.

512. *Allylamine.* B. p. 54·5°/758 mm.; *M* 57·10; n_C 1·41747, n_D 1·42051, n_F 1·42792, $n_{G'}$ 1·43363; R_C 18·86, R_D 18·98, R_F 19·27, $R_{G'}$ 19·50; $Mn_D^{20°}$ 81·11. Densities determined: $d_{4°}^{20°}$ 0·7621, $d_{4°}^{41·3°}$ 0·7407. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
24·5°	17·11	0·7576	24·27	167·4	31·1°	16·76	0·7510	23·57	167·7
28·3	16·91	0·7538	23·87	167·5	41·6	15·94	0·7404	22·10	167·5
								Mean	167·5

513. *Ethylenediamine.* B. p. 117°/750 mm.; *M*, 60·10; n_C 1·45399, n_D 1·45677, n_F 1·46344, $n_{G'}$ 1·46869; R_C 18·13, R_D 18·23, R_F 18·45, $R_{G'}$ 18·64; $Mn_D^{20°}$ 87·55. Densities determined: $d_{4°}^{20°}$ 0·8977, $d_{4°}^{40·7°}$ 0·8799, $d_{4°}^{60·6°}$ 0·8615, $d_{4°}^{83·3°}$ 0·8400. Apparatus *D*.

21·3°	18·88	0·8966	41·80	170·4	63·1°	16·92	0·8593	35·91	171·2
40·7	17·99	0·8799	39·09	170·8	86·1	15·82	0·8384	32·75	171·7
								Mean	171·0

514. *Aniline.* B. p. 184·5°/750 mm.; *M* 93·13; n_C 1·57865, n_D 1·58547, n_F 1·60343; R_C 30·27, R_D 30·56, R_F 31·31; $Mn_D^{20°}$ 147·66. Densities determined: $d_{4°}^{20°}$ 1·0221, $d_{4°}^{40·2°}$ 1·0052, $d_{4°}^{60·1°}$ 0·9889, $d_{4°}^{86·0°}$ 0·9669. Apparatus *A*.

19·6°	20·88	1·0224	39·97	229·1	61·3°	19·23	0·9879	35·57	230·2
40·0	20·05	1·0050	37·73	229·7	85·8	18·35	0·9671	33·23	231·2
								Mean	230·1

The surface-tension measurements were not altogether satisfactory and will be repeated by the method of maximum bubble pressure.

515. *Benzylamine.* B. p. 185°/767 mm.; *M* 107·15; n_C 1·53895, n_D 1·54380, n_F 1·55656, $n_{G'}$ 1·56656; R_C 34·20, R_D 34·45, R_F 35·12, $R_{G'}$ 35·64; $Mn_D^{20°}$ 165·45. Densities determined: $d_{4°}^{20°}$ 0·9816, $d_{4°}^{42·0°}$ 0·9653, $d_{4°}^{61·0°}$ 0·9489, $d_{4°}^{86·6°}$ 0·9272. Apparatus *D*.

21·1°	16·44	0·9807	39·82	274·4	62·4°	14·82	0·9478	34·69	274·4
41·9	15·62	0·9654	37·24	274·2	88·0	13·86	0·9261	31·70	274·5
								Mean	274·4

516. cyclo*Hexylamine.* B. p. 133°/756 mm.; *M* 99·17; n_C 1·45665, n_D 1·45926, n_F 1·46539, $n_{G'}$ 1·47001; R_C 31·13, R_D 31·29, R_F 31·64, $R_{G'}$ 31·91; $Mn_D^{20°}$ 144·72. Densities determined: $d_{4°}^{20°}$ 0·8671, $d_{4°}^{40·6°}$ 0·8498, $d_{4°}^{62·3°}$ 0·8307, $d_{4°}^{85·3°}$ 0·8106. Apparatus *A*.

16·2°	19·80	0·8703	32·27	271·6	41·1°	18·43	0·8494	29·31	271·7
17·9	19·70	0·8689	32·05	271·6	61·2	17·20	0·8316	26·78	271·3
22·9	19·48	0·8646	31·54	271·8	87·0	15·80	0·8091	23·94	271·1
								Mean	271·5

517. *Diethylamine.* B. p. 55°/756 mm.; *M* 73·14; n_C 1·38417, n_D 1·38637, n_F 1·39167, $n_{G'}$ 1·39560; R_C 24·18, R_D 24·30, R_F 24·60, $R_{G'}$ 24·82; $Mn_D^{20°}$ 101·40. Densities determined: $d_{4°}^{20°}$ 0·7074, $d_{4°}^{41·8°}$ 0·6849. Apparatus *A* *. Apparatus *D* **.

24·9°	15·14	0·7023	19·91	220·3 *	23·8°	11·59	0·7034	20·13	220·6**
41·0	14·05	0·6852	18·03	220·4 *	41·3	10·60	0·6851	17·93	220·2**
16·4	11·79	0·7114	20·71	220·1**				Mean	220·3

518. *Di*-n-*propylamine.* B. p. 108°/751 mm.; *M* 101·19; n_C 1·40278, n_D 1·40499, n_F 1·41039, $n_{G'}$ 1·41425; R_C 33·36, R_D 33·51, R_F 33·91, $R_{G'}$ 34·19; $Mn_D^{20°}$ 142·17. Densities determined: $d_{4°}^{20°}$ 0·7400, $d_{4°}^{41·1°}$ 0·7213, $d_{4°}^{59·9°}$ 0·7043, $d_{4°}^{86·1°}$ 0·6798. Apparatus *A*.

16·9°	16·63	0·7428	23·13	298·8	61·7°	14·05	0·7027	18·49	298·9
24·5	16·17	0·7359	22·28	298·7	85·2	12·67	0·6806	16·15	298·7
41·3	15·38	0·7211	20·77	299·5				Mean	298·9

519. *Diisopropylamine.* B. p. 83·5°/765 mm.; *M* 101·19; n_C 1·39021, n_D 1·39236, n_F 1·39762, $n_{G'}$ 1·40177; R_C 33·48, R_D 33·64, R_F 34·04, $R_{G'}$ 34·35; $Mn_D^{20°}$ 140·90. Densities determined: $d_{4°}^{20°}$ 0·7169, $d_{4°}^{41·2°}$ 0·6980, $d_{4°}^{61·4°}$ 0·6781. Apparatus *A*.

16·0°	14·85	0·7206	20·04	297·1	41·5°	13·27	0·6977	17·34	296·3
26·3	14·35	0·7111	19·11	297·5	61·5	11·98	0·6777	15·20	295·6
								Mean	296·6

520. *Di*-n-*butylamine*. B. p. 159°/761 mm.; *M* 129·24; n_C 1·41539, n_D 1·41766, n_F 1·42310, $n_{G'}$ 1·42725; R_C 42·61, R_D 42·82, R_F 43·30, $R_{G'}$ 43·68; $Mn_D^{20°}$ 183·22. Densities determined: $d_{4°}^{20°}$ 0·7601, $d_{4°}^{41·7°}$ 0·7435, $d_{4°}^{61·0°}$ 0·7277, $d_{4°}^{84·9°}$ 0·7081. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
17·7°	17·39	0·7619	24·81	378·6	60·4°	15·19	0·7282	20·71	378·6
40·9	16·24	0·7441	22·63	378·8	86·2	13·84	0·7071	18·32	378·6
								Mean	378·7

521. *Diisobutylamine*. B. p. 137°/742 mm.; *M* 129·24; n_C 1·40679, n_D 1·40900, n_F 1·41448, $n_{G'}$ 1·41831; R_C 42·63, R_D 42·83, R_F 43·34, $R_{G'}$ 43·70; $Mn_D^{20°}$ 182·10. Densities determined: $d_{4°}^{20°}$ 0·7460, $d_{4°}^{40·8°}$ 0·7297, $d_{4°}^{62·0°}$ 0·7128, $d_{4°}^{86·3°}$ 0·6906. Apparatus *D*.

15·1°	12·19	0·7499	22·58	375·7	60·2°	10·44	0·7142	18·42	374·9
23·9	11·93	0·7429	21·89	376·3	86·7	9·46	0·6903	16·13	375·2
40·8	11·26	0·7297	20·29	375·9				Mean	375·6

522. *Di*-sec.-*butylamine*. B. p. 135°/765 mm.; *M* 129·24; n_C 1·40875, n_D 1·41092, n_F 1·41624, $n_{G'}$ 1·42017; R_C 42·39, R_D 42·58, R_F 43·06, $R_{G'}$ 43·43; $Mn_D^{20°}$ 182·34. Densities determined: $d_{4°}^{20°}$ 0·7534, $d_{4°}^{40·8°}$ 0·7362, $d_{4°}^{61·0°}$ 0·7192, $d_{4°}^{85·1°}$ 0·6989. Apparatus *D*.

14·6°	12·41	0·7579	23·28	374·4	40·9°	11·36	0·7361	20·65	374·3
22·0	12·09	0·7518	22·45	374·2	60·6	10·49	0·7195	18·64	373·2
								Mean	374·0

523. *Di*-n-*amylamine*. B. p. 67°/4 mm.; *M* 157·29; n_C 1·42494, n_D 1·42722, n_F 1·43280, $n_{G'}$ 1·43679; R_C 51·74, R_D 51·99, R_F 52·58, $R_{G'}$ 53·01; $Mn_D^{20°}$ 224·48. Densities determined: $d_{4°}^{20°}$ 0·7771, $d_{4°}^{60·8°}$ 0·7456, $d_{4°}^{86·0°}$ 0·7269, $d_{4°}^{119·8°}$ 0·7018. Apparatus *A*.

14·1°	18·20	0·7816	26·64	457·2	87·4°	14·82	0·7258	20·14	459·1
25·9	17·83	0·7726	25·79	458·8	121·1	13·21	0·7008	17·34	458·0
60·4	16·04	0·7459	22·40	458·8				Mean	458·6

524. *Diisoamylamine*. B. p. 186—186·5°/756 mm.; *M* 157·29; n_C 1·42119, n_D 1·42346, n_F 1·42899, $n_{G'}$ 1·43301; R_C 51·77, R_D 52·02, R_F 52·61, $R_{G'}$ 53·04; $Mn_D^{20°}$ 223·90. Densities determined: $d_{4°}^{20°}$ 0·7708, $d_{4°}^{40·7°}$ 0·7552, $d_{4°}^{60·1°}$ 0·7405, $d_{4°}^{85·5°}$ 0·7213. Apparatus *D*.

14·2°	12·92	0·7752	24·73	452·5	60·4°	11·35	0·7403	20·75	453·5
23·3	12·76	0·7683	24·21	454·1	86·5	10·50	0·7205	18·68	453·9
40·5	12·08	0·7554	22·54	453·7				Mean	453·5

525. *Dicyclohexylamine*. B. p. 113·5°/9 mm.; *M* 181·31; n_C 1·48194, n_D 1·48454, n_F 1·49080, $n_{G'}$ 1·49560; R_C 56·65, R_D 56·91, R_F 57·54, $R_{G'}$ 58·02; $Mn_D^{20°}$ 269·15. Densities determined: $d_{4°}^{20°}$ 0·9123, $d_{4°}^{40·8°}$ 0·8978, $d_{4°}^{60·1°}$ 0·8842, $d_{4°}^{85·3°}$ 0·8662. Apparatus *A*.

15·1°	15·13	0·9157	34·22	478·9	60·5°	13·61	0·8839	29·71	478·9
20·4	14·99	0·9120	33·76	479·2	87·9	12·74	0·8644	27·20	479·0
40·4	14·32	0·8970	31·75	479·4				Mean	479·1

526. *Ethyl* N-*methylcarbamate*. B. p. 169·5°/769 mm.; *M* 103·18; n_C 1·41594, n_D 1·41826, n_F 1·42386, $n_{G'}$ 1·42798; R_C 25·59, R_D 25·73, R_F 26·03, $R_{G'}$ 26·25; $Mn_D^{20°}$ 146·34. Densities determined: $d_{4°}^{20°}$ 1·0115, $d_{4°}^{41·2°}$ 0·9924, $d_{4°}^{61·1°}$ 0·9744, $d_{4°}^{86·8°}$ 0·9503. Apparatus *D*.

23·0°	12·99	1·0088	32·36	242·6	61·0°	11·85	0·9745	28·52	244·7
25·4	12·92	1·0066	32·12	244·0	86·1	11·04	0·9507	25·92	244·9
40·9	12·44	0·9927	29·80	242·9				Mean	243·8

527. *Ethyl* N-*ethylcarbamate*. B. p. 175°/748 mm.; *M* 117·15; n_C 1·41919, n_D 1·42151, n_F 1·42713, $n_{G'}$ 1·43126; R_C 30·25, R_D 30·40, R_F 30·75, $R_{G'}$ 31·01; $Mn_D^{20°}$ 166·53. Densities determined: $d_{4°}^{20°}$ 0·9784, $d_{4°}^{41·6°}$ 0·9593, $d_{4°}^{60·4°}$ 0·9425, $d_{4°}^{86·5°}$ 0·9177. Apparatus *A*.

21·1°	16·54	0·9774	30·27	281·1	61·3°	14·91	0·9417	26·29	281·7
41·7	15·73	0·9592	28·25	281·6	86·9	14·00	0·9173	24·05	282·8
								Mean	281·7

528. N-*Nitrosomethylaniline*. B. p. 120°/13 mm.; *M* 136·15; n_C 1·56992, n_D 1·57764, n_F 1·59901 (line rather faint); R_C 39·54, R_D 39·97, R_F 41·18; $Mn_D^{20°}$ 214·79. Densities determined: $d_{4°}^{20°}$ 1·1297, $d_{4°}^{41·4°}$ 1·1113, $d_{4°}^{61·5°}$ 1·0941, $d_{4°}^{86·9°}$ 1·0722. Apparatus *D*.

18·8°	16·23	1·1307	45·32	312·4	60·9°	14·94	1·0946	40·39	313·6
41·0	15·51	1·1116	42·58	312·9	87·3	14·10	1·0719	37·33	313·9
								Mean	313·2

529. *Monomethylaniline*. B. p. 193°/738 mm.; *M* 107·15; n_C 1·56411, n_D 1·57094, n_F 1·58899, $n_{G'}$ 1·60447 (line very faint); R_C 35·32, R_D 35·67, R_F 36·60, $R_{G'}$ 37·38; $Mn_D^{20°}$ 168·32. Densities determined: $d_{4°}^{20°}$ 0·9867, $d_{4°}^{40·2°}$ 0·9707, $d_{4°}^{60·3°}$ 0·9555, $d_{4°}^{85·5°}$ 0·9350. Apparatus *A*.

12·2°	21·97	0·9929	40·85	272·8	60·7°	19·69	0·9558	35·24	273·1
17·7	21·82	0·9885	40·39	273·1	86·5	18·59	0·9342	32·52	273·9
40·1	20·75	0·9708	37·72	273·5				Mean	273·3

530. N-*Nitrosoethylaniline.* B. p. 131°/20 mm.; M 150·18; n_C 1·55269, n_D 1·55969, n_F 1·57894 (line rather faint); R_C 44·15, R_D 44·61, R_F 45·86; $Mn_D^{20°}$ 234·24. Densities determined: $d_{4°}^{40·7°}$ 1·0881, $d_{4°}^{40·7°}$ 1·0704, $d_{4°}^{61·9°}$ 1·0525, $d_{4°}^{86·0°}$ 1·0297. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
12·3°	20·63	1·0947	42·29	349·8	61·2°	18·62	1·0531	36·72	351·0
18·1	20·26	1·0897	41·54	349·9	85·8	17·71	1·0299	34·15	352·5
42·4	19·44	1·0689	38·91	350·9				Mean	350·8

531. *Monoethylaniline.* B. p. 202·5°/750 mm.; M 121·18; n_C 1·54738, n_D 1·55397, n_F 1·57030, $n_{G'}$ 1·58444 (line rather faint); R_C 40·05, R_D 40·45, R_F 41·43, $R_{G'}$ 42·27; $Mn_D^{20°}$ 188·32. Densities determined: $d_{4°}^{20°}$ 0·9601, $d_{4°}^{41·5°}$ 0·9431, $d_{4°}^{61·7°}$ 0·9273, $d_{4°}^{86·1°}$ 0·9082. Apparatus *A*.

20·5°	20·47	0·9597	36·79	311·0	62·5°	18·57	0·9267	32·22	311·6
41·3	19·62	0·9433	34·66	311·7	87·6	17·46	0·9074	29·67	311·7
								Mean	311·5

532. *Mono*-n-*propylaniline.* B. p. 219°/758 mm. and 96°/9 mm.; M 135·20; n_C 1·53596, n_D 1·54217, n_F 1·55729, $n_{G'}$ 1·56991; R_C 44·72, R_D 45·15, R_F 46·19, $R_{G'}$ 47·05; $Mn_D^{20°}$ 208·51. Densities determined: $d_{4°}^{20°}$ 0·9426, $d_{4°}^{40·0°}$ 0·9276, $d_{4°}^{60·1°}$ 0·9119, $d_{4°}^{85·9°}$ 0·8921. Apparatus *C*.

20·9°	15·55	0·9419	34·77	348·6	61·4°	14·26	0·9109	30·84	349·8
41·0	14·87	0·9268	32·72	348·9	87·1	13·45	0·8913	28·46	350·4
								Mean	349·4

533. *Mono*-n-*butylaniline.* B. p. 237—238°/760 mm. and 105°/3 mm.; M 149·23; n_C 1·52803, n_D 1·53342, n_F 1·54750, $n_{G'}$ 1·55943; R_C 49·38, R_D 49·80, R_F 50·90, $R_{G'}$ 51·81; $Mn_D^{20°}$ 228·83. Densities determined: $d_{4°}^{20°}$ 0·9305, $d_{4°}^{40·0°}$ 0·9157, $d_{4°}^{59·1°}$ 0·9107, $d_{4°}^{86·2°}$ 0·8812. Apparatus *C*.

20·9°	15·36	0·9298	33·90	389·1	59·5°	14·25	0·9014	30·50	389·0
40·7	14·73	0·9152	32·00	387·8	86·9	13·44	0·8807	28·10	390·0
								Mean	389·0

534. *Triethylamine.* B. p. 89·5°/759 mm.; M 101·19; n_C 1·39859, n_D 1·40101, n_F 1·40670, $n_{G'}$ 1·41099; R_C 33·62, R_D 33·79, R_F 34·23, $R_{G'}$ 34·54; $Mn_D^{20°}$ 141·77. Densities determined: $d_{4°}^{20°}$ 0·7275, $d_{4°}^{41·7°}$ 0·7087, $d_{4°}^{60·6°}$ 0·6912. Apparatus *C*.

22·3°	11·91	0·7255	20·51	296·8	62·0°	10·12	0·6899	16·57	296·7
42·2	10·98	0·7083	18·46	296·5				Mean	296·7

535. *Tri*-n-*propylamine.* B. p. 156·5°/760 mm.; M 143·27; n_C 141471, n_D 1·41706, n_F 1·42279, $n_{G'}$ 1·42718; R_C 47·44, R_D 47·68, R_F 48·25, $R_{G'}$ 48·69; $Mn_D^{20°}$ 203·03. Densities determined: $d_{4°}^{20°}$ 0·7558, $d_{4°}^{42·0°}$ 0·7411, $d_{4°}^{62·0°}$ 0·7258, $d_{4°}^{87·9°}$ 0·7056. Apparatus *A*.

24·5°	15·95	0·7526	22·48	414·4	60·1°	14·16	0·7271	19·28	412·9
41·3	15·05	0·7416	20·90	413·1	84·3	12·98	0·7082	17·21	412·1
								Mean	413·1

536. *Tri*-n-*butylamine.* B. p. 212°/761 mm.; M 185·35; n_C 1·42727, n_D 1·42967, n_F 1·43547, $n_{G'}$ 1·43975; R_C 61·20, R_D 61·50, R_F 62·22, $R_{G'}$ 62·75; $Mn_D^{20°}$ 264·99. Densities determined: $d_{4°}^{20°}$ 0·7781, $d_{4°}^{41·4°}$ 0·7638, $d_{4°}^{60·0°}$ 0·7500, $d_{4°}^{87·1°}$ 0·7300. Apparatus *B*.

22·9°	13·52	0·7761	24·60	531·9	61·8°	12·17	0·7487	21·36	532·2
42·0	12·82	0·7634	22·91	531·4	89·9	11·13	0·7280	19·00	531·6
								Mean	531·8

537. *Tri*-n-*amylamine.* B. p. 109°/5 mm.; M 227·42; n_C 1·43426, n_D 1·43665, n_F 1·44238, $n_{G'}$ 1·44666; R_C 74·94, R_D 75·31, R_F 76·16, $R_{G'}$ 76·80; $Mn_D^{20°}$ 326·73. Densities determined: $d_{4°}^{20°}$ 0·7907, $d_{4°}^{40·1°}$ 0·7761, $d_{4°}^{60·7°}$ 0·7614, $d_{4°}^{86·8°}$ 0·7428. Apparatus *A*.

12·1°	18·01	0·7964	26·86	650·1	61·1°	15·93	0·7611	22·70	652·2
26·4	17·53	0·7861	25·80	652·0	87·5	14·77	0·7423	20·53	652·3
41·5	16·82	0·7751	24·41	652·2				Mean	651·8

538. *Triisoamylamine.* B. p. 94°/4 mm.; M 227·42; n_C 1·43066, n_D 1·43305, n_F 1·43875, $n_{G'}$ 1·44308; R_C 74·97, R_D 75·33, R_F 76·19, $R_{G'}$ 76·84; $Mn_D^{20°}$ 325·92. Densities determined: $d_{4°}^{20°}$ 0·7848, $d_{4°}^{40·6°}$ 0·7700, $d_{4°}^{60·5°}$ 0·7557, $d_4^{86·7°}$ 0·7364. Apparatus *B*.

14·7°	13·44	0·7886	24·85	643·9	60·7°	11·81	0·7554	20·92	643·9
40·8	12·51	0·7699	22·58	643·9	86·5	10·99	0·7365	18·98	644·5
								Mean	644·1

539. *Benzyldiethylamine.* B. p. 209—210°/757 mm. and 125°/12 mm.; M 163·25; n_C 1·49334, n_D 1·49734, n_F 1·50736, $n_{G'}$ 1·51546; R_C 53·11, R_D 53·47, R_F 54·39, $R_{G'}$ 55·12; $Mn_D^{20°}$ 244·43. Densities determined: $d_{4°}^{20°}$ 0·8938, $d_{4°}^{40·5°}$ 0·8783, $d_{4°}^{60·5°}$ 0·8627, $d_{4°}^{87·5°}$ 0·8416. Apparatus *F*.

18·1°	14·44	0·8953	30·10	427·1	60·3°	12·94	0·8629	26·00	427·2
19·9	14·34	0·8939	29·84	426·9	86·5	12·09	0·8424	23·77	427·6
40·9	13·52	0·8780	27·64	426·3				Mean	427·0

540. *Ethyl nitrilotricarboxylate.* B. p. 143°/10 mm.; M 233·22; n_C 1·42665, n_D 1·42897, n_F 1·43456, $n_{G'}$ 1·43877; R_C 52·53, R_D 52·88, R_F 53·38, $R_{G'}$ 53·82; $Mn_D^{20°}$ 333·51. Densities determined: $d_4^{20°}$ 1·1392, $d_4^{40·0°}$ 1·1198, $d_4^{60·9°}$ 1·0994, $d_4^{86·1°}$ 1·0749. Apparatus *E*.

t.	H.	$d_{4°}^{t°}$.	γ.	P.	t.	H.	$d_{4°}^{t°}$.	γ.	P.
18·9°	13·11	1·1403	34·82	496·8	60·2°	11·84	1·1101	30·35	497·3
20·5	13·03	1·1387	34·81	497·5	86·8	11·15	1·0742	27·89	498·9
40·2	12·52	1·1196	32·65	497·9				Mean	497·7

541. *Dimethylaniline.* B. p. 194°/760 mm.; M 121·18; n_C 1·55110, n_D 1·55776, n_F 1·57051, $n_{G'}$ 1·59132 (line very faint); R_C 40·40, R_D 40·81, R_F 41·84, $R_{G'}$ 42·80; $Mn_D^{20°}$ 188·77. Densities determined: $d_4^{20°}$ 0·9571, $d_4^{62·0°}$ 0·9255, $d_4^{86·2°}$ 0·9055, $d_4^{119·7°}$ 0·8783. Apparatus *B*.

19·5°	16·11	0·9575	36·17	310·4	86·8°	13·65	0·9050	28·97	310·6
66·3	14·39	0·9222	31·12	310·4	121·7	12·37	0·8768	25·43	310·4
								Mean	310·5

542. *Diethylaniline.* B. p. 214·5°/748 mm. and 86·5°/6 mm.; M 149·23; n_C 1·53578, n_D 1·54178, n_F 1·55773, $n_{G'}$ 1·57227 (line faint); R_C 49·74, R_D 50·20, R_F 51·42, $R_{G'}$ 52·52; $Mn_D^{20°}$ 230·08. Densities determined: $d_4^{20°}$ 0·9353, $d_4^{40·8°}$ 0·9195, $d_4^{61·3°}$ 0·9042, $d_4^{85·0°}$ 0·8851. Apparatus *C*.

19·9°	15·55	0·9354	34·53	386·7	60·7°	14·10	0·9047	30·28	386·9
40·9	14·81	0·9194	32·33	387·0	86·8	13·13	0·8837	27·55	386·9
								Mean	386·9

543. *Di-n-propylaniline.* B. p. 242°/758 mm. and 95°/4 mm.; M 177·28; n_C 1·52333, n_D 1·52873, n_F 1·54292, $n_{G'}$ 1·55539 (line very faint); R_C 59·05. R_D 59·56, R_F 60·89, $R_{G'}$ 62·05; $Mn_D^{20°}$ 271·01. Densities determined: $d_4^{20°}$ 0·9176, $d_4^{41·2°}$ 0·9021. $d_4^{61·1°}$ 0·8879, $d_4^{85·8°}$ 0·8695. Apparatus *C*.

22·0°	15·08	0·9160	32·79	463·1	60·4°	13·67	0·8884	28·83	462·4
24·3	14·95	0·9145	32·46	462·7	87·5	12·84	0·8683	26·47	463·1
42·4	14·39	0·9012	30·79	463·4				Mean	463·0

544. *Di-n-butylaniline.* B. p. 269—270°/760 mm.; M 205·33; n_C 1·51444, n_D 1·51929, n_F 1·53246, $n_{G'}$ 1·54349 (line very faint); R_C 68·29, R_D 68·84, R_F 70·30, $R_{G'}$ 71·51; $Mn_D^{20°}$ 311·96. Densities determined: $d_4^{20°}$ 0·9058, $d_4^{41·3°}$ 0·8905, $d_4^{61·0°}$ 0·8763, $d_4^{85·4°}$ 0·8581. Apparatus *C*.

15·1°	15·22	0·9083	32·82	541·1	61·6°	13·61	0·8759	28·30	540·7
40·7	14·35	0·8901	30·32	541·3	87·8	12·80	0·8567	26·03	541·4
								Mean	541·1

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369. *Physical Properties and Chemical Constitution. Part XXIII. Miscellaneous Compounds. Investigation of the So-called Co-ordinate or Dative Link in Esters of Oxy-acids and in Nitro-paraffins by Molecular Refractivity Determinations. Atomic, Structural, and Group Parachors and Refractivities.*

By ARTHUR I. VOGEL.

New determinations of the refractivities at 20° and of the parachors of esters of dichloroacetic and trichloroacetic acid have been made with the object of investigating the influence of two or three chlorine atoms respectively attached to the same carbon atom; the resulting constants were not exact multiples of those found for chlorine in monosubstituted compounds (Part XIV, this vol., p. 644). Similarly, the constants for $\geqslant$CH evaluated from measurements upon trialkyl orthoformates, $CH(OR)_3$, were not exactly equal to (C + H) deduced from aliphatic hydrocarbons (Part IX, *J.*, 1946, 133).

An analysis of the experimental results for dialkyl sulphites and sulphates and of trialkyl orthophosphates (Part VII, *J.*, 1943, 16) led to constants for the >SO, $>SO_2$, and $\geqslant$PO groups, but no evidence from parachors or refractivities of the presence of covalent double bonds was apparent. Similar results were obtained from $SO_2Cl_2 - SOCl_2$ and from $POCl_3 - PCl_3$. The physical constants of the −N=O group in nitrosoamines, deduced from $R_2N{\cdot}NO + H - R_2NH$, were not comparable with those for $\geqslant$PO.

Determinations have also been made of the parachors and refractivities of dialkyl nitrosoamines, nitro-paraffins, alkyl nitrites, alkyl nitrates, dialkyl carbonates, alkyl thiocyanates and *iso*thiocyanates, and alkyl xanthates, and the constants of the following groups were evaluated: $-N(NO)$, $-NO_2$, $-ONO$, $-NO_3$, −SCN, −NCS, and >CS. The constants for >CO in dialkyl carbonates were almost identical with those previously found for aliphatic ketones (Part XI, this vol., p. 610), and the constants for −CN in alkyl thiocyanates (-SCN − S,

in sulphides) were in good agreement with those deduced from aliphatic nitriles (Part XVII, this vol., p. 674).

The parachor and refractivity constants for the covalent double bonds C=C, C=O, C=S, and N=O are not identical.

Revised values for the atomic, structural, and group parachors and refractivities so far determined are tabulated; these supersede those of Sugden and of Eisenlohr.

The results, particularly for the molecular refractivities, do not support the view of Phillips, Hunter, and Sutton (*J.*, 1945, 146) that the esters and acid chlorides of the oxy-acids of sulphur and phosphorus contain covalent double bonds.

In the deduction of the parachor and refractivities of the halogens, the author (*loc. cit.*) has employed compounds in which only one halogen atom is attached to a carbon atom. Other workers have not confined their calculations to such simple compounds: for instance, Eisenlohr (*Z. physikal. Chem.*, 1910, **75**, 594) includes ethylidene chloride, " dichloroacetic ester ", ethyl dichloropropionate, chloroform, chloral, butyl chloral, carbon tetrachloride, perchloroethylene, and pentachloroethane, whilst Sugden (" The Parachor and Valency ", Routledge, 1930, p. 37) includes carbon tetrachloride, chloroform, methylene chloride, acetylene tetrachloride, and ethylidene chloride. The possibility that the attachment of two or more halogen atoms or groups to the same carbon atom may be partly responsible for the variations found for the constants appears to have been overlooked by previous investigators; preliminary experiments are now described which have been designed to study the effect of poly-groupings. Alkyl dichloroacetates may be readily prepared in a state of purity; the contributions of Cl_2 to the physical properties may be computed from the relationship:

$$Cl_2 = CHCl_2{\cdot}CO_2R + H - 0{\cdot}5(CH_2{\cdot}CO_2R)_2$$

The constants for H are from Part IX (*loc. cit.*) and the experimental data for dialkyl succinates have been taken from Part XIII (this vol., p. 624). The results are given in Table I. It will be noted that the parachor is slightly lower and the refractivities appreciably higher than those deduced for monochloro-compounds, the values for which are included in the table for purposes of comparison. The results obtained for methylene chloride ($CH_2Cl_2 - CH_2$), ethylidene chloride ($CH_3{\cdot}CHCl_2 + H - C_2H_5$) and acetylene tetrachloride ($CHCl_2{\cdot}CHCl_2 + 2H - 2CH_2$) are also included; the refractivities for these compounds are appreciably lower than those deduced for the dichloroacetates and, in the author's view, these figures are less trustworthy owing to the difficulty of preparing and *keeping* these polyhalogenated hydrocarbons in a state of purity.

Table I.

Values for Cl_2 *from compounds containing the* Cl_2 *grouping.*

Compound.	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$
$CHCl_2{\cdot}CO_2Me$	106·9	11·99	12·05	12·20	12·31	99·96
$CHCl_2{\cdot}CO_2Et$	109·3	11·98	12·04	12·19	12·30	99·61
$CHCl_2{\cdot}CO_2Pr^n$	107·2	12·00	12·05	12·21	12·31	99·57
$CHCl_2{\cdot}CO_2Bu^n$	105·9	11·92	11·98	12·12	12·24	99·72
Mean (Cl_2)	107·3	11·973	12·030	12·180	12·290	99·72
CH_2Cl_2	107·5	11·68	11·73	11·88	11·98	100·21
$CH_3{\cdot}CHCl_2$	107·9	11·76	11·82	11·97	12·08	98·86
$CHCl_2{\cdot}CHCl_2$	104·6	11·64	11·68	11·82	11·92	102·29
Mean Cl (from monohalogen compounds)	55·2	5·821	5·844	5·918	5·973	50·41

The constants of the Cl_3 group were obtained from measurements upon alkyl trichloroacetates:

$$Cl_3 = CCl_3{\cdot}CO_2R + 2H - 0{\cdot}5(CH_2{\cdot}CO_2R)_2$$

The results, as well as those for the unstable chloroform ($CHCl_3 + H - CH_2$) and the somewhat more stable methylchloroform ($CH_3{\cdot}CCl_3 + 2H - C_2H_5$), are collected in Table II; it will be

Table II.

Values for Cl_3 *from compounds containing the* Cl_3 *grouping.*

Compound.	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$CCl_3{\cdot}CO_2Me$	156·7	17·94	18·03	18·28	18·42	149·68
$CCl_3{\cdot}CO_2Et$	159·4	18·10	18·19	18·43	18·58	148·84
$CCl_3{\cdot}CO_2Pr^n$	158·6	17·94	18·03	18·28	18·41	148·84
$CCl_3{\cdot}CO_2Bu^n$	158·0	17·96	18·06	18·31	18·46	148·93
Mean (Cl_3)	158·2	17·985	18·078	18·325	18·468	149·07
$CHCl_3$	158·9	17·67	17·75	17·97	18·12	149·51
$CH_3{\cdot}CCl_3$	160·7	17·85	17·96	18·19	18·33	148·06

observed that the parachor is lower and the refractivities are higher per chlorine atom than those for monochloro-compounds. Similar effects are exhibited by carbon tetrachloride (CCl_4 — C), which gives for Cl_4: P 212·4; R_C 23·76; R_D 23·86; R_F 24·26; R_G 24·42; $Mn_D^{20°}$ 198·94.

Only a few polybromo-compounds have so far been examined, with the following results:

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Br_2 from CH_2Br_2	135·1	17·14	17·25	17·55	17·79	247·36
Br_2 from $CHBr_2{\cdot}CHBr_2$	—	17·26	17·37	17·67	—	259·51
Br_2 from $CHBr_3$	203·5	26·06	26·24	26·72	27·09	380·68
Mean Br (from monohalogen compounds)	68·8	8·681	8·741	8·892	9·011	118·07

No trustworthy conclusions can be drawn from these results alone, particularly from bromoform which is known to be unstable in the pure state, but it would appear that the parachor and the refractivities are lower for compounds with the Br_2 grouping.

By combining the author's density determinations for methylene iodide with the refractive index measurements by Timmermans and Hennaut-Roland (*J. Chim. physique*, 1932, **29**, 529), the values for I_2 are found to be: R_C 27·58, R_D 27·89, and R_F 28·73. The constants determined from monoiodo-compounds (Part XIV, *loc. cit.*) were: R_C 13·825, R_D 13·954, and R_F 14·310.

In Part XII (this vol., p. 616) it was shown that the constants for oxygen in dialkyl ethers were greater than those in acetals, $CHR'(OR)_2$; this is probably another example of the influence of two groupings attached to the same carbon atom upon the physical properties. The acetals $CH_2(OR)_2$ are of particular interest in that they permit the calculation of the contributions of $(OR)_2$ to the physical constants by mere subtraction of the constants for CH_2 (Part IX, *loc. cit.*). To investigate the effect of three alkoxyl groups attached to the same carbon atom, the physical properties of three trialkyl orthoformates were measured and the values for $\rangle CH$ computed from:

$$\rangle CH = CH(OR)_3 - 3(OR)$$

The results are given in Table III; it will be noted that the mean values for $\rangle CH$ thus obtained are lower than those for (C + H) derived from aliphatic hydrocarbons (Part IX, *loc. cit.*).

TABLE III.

Values for $\rangle CH$ *from trialkyl orthoformates*, $CH(OR)_3$.

Compound.	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$CH(OEt)_3$	22·1	3·46	3·48	3·51	3·53	22·41
$CH(OPr^n)_3$	20·4	3·52	3·55	3·58	3·61	22·52
$CH(OBu^n)_3$	19·3	3·51	3·55	3·56	3·58	22·48
Mean ($\rangle CH$)	20·6	3·497	3·527	3·550	3·573	22·47
C + H (Part IX)	24·3	3·598	3·619	3·644	3·695	23·15

The parachors and the refractivities of thionyl chloride, sulphuryl chloride, phosphorus trichloride, and phosphorus oxychloride were determined primarily with the object of obtaining new evidence on the nature of the oxy-bond from considerations of the molecular refractivities. The results are collected below, including the differences (SO_2Cl_2 — $SOCl_2$) and ($POCl_3$ — PCl_3).

	P.	R_C.	R_D.	R_F.	R_G.	$Mn_D^{20°}$.
SO_2Cl_2	188·4	21·31	21·43	21·70	21·92	194·80
$SOCl_2$	174·7	21·95	22·12	22·56	22·98	180·06
O (SO_2Cl_2 — $SOCl_2$)	13·7	−0·64	−0·69	−0·86	−1·06	14·74
$POCl_3$	218·6	24·97	25·05	25·36	25·59	224·03
PCl_3	201·6	26·08	26·27	26·74	27·11	208·04
O($POCl_3$ — PCl_3)	17·0	−1·11	−1·22	−1·38	−1·52	15·99

The negative values for the refractivities are particularly noteworthy. Similar calculations have been made from the data for dialkyl sulphates and dialkyl sulphites R_2SO_4 — R_2SO_3 (Part VII, *loc. cit.*) and the results are presented in Table IV. These figures are more trustworthy owing to

TABLE IV.

Constants for oxygen from R_2SO_4 — R_2SO_3.

R.	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Me	18·2	−0·07	−0·08	−0·15	−0·19	19·79
Et	18·8	−0·11	−0·14	−0·20	−0·26	20·37
Pr^n	16·8	−0·30	−0·33	−0·40	−0·46	20·80
Bu^n	17·4	−0·21	−0·25	−0·32	−0·36	23·40

the difficulties attending measurements with acid chlorides. The only refractivity data available for trialkyl phosphites * are those of Jones, Davies, and Dyke (*J. Physical Chem.*, 1933, **37**, 583) for triethyl and tri-*n*-amyl phosphites; these lead to the following values for R_3PO_4 (VII, **44** and VII, **49**) − R_3PO_3:

	R_C.	R_D.	R_F.
$Et_3PO_4 - Et_3PO_3$	−1·13	−1·23	−1·36
$Am^n_3PO_4 - Am^n_3PO_3$	−1·29	−1·33	−1·48

The constants for $>SO_2$ in dialkyl sulphates may be computed from the relationship $>SO_2 = SO_2(OR)_2 - \{CH_2(OR)_2 - CH_2\}$, and those for $>SO$ in dialkyl sulphites may be similarly calculated from $>SO = SO(OR)_2 - \{CH_2(OR)_2 - CH_2\}$. The data for the acetals are given in Part XII (*loc. cit.*). The results are collected in Tables V and VI. The differences

TABLE V.

Values for $>SO_2$ *from dialkyl sulphates,* $SO_2(OR)_2$.

Compound.	*P*.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$SO_2(OMe)_2$	87·6	7·79	7·83	7·87	7·91	92·64
$SO_2(OEt)_2$	87·5	7·87	7·89	7·94	7·98	93·44
$SO_2(OPr^n)_2$	83·8	7·77	7·81	7·85	7·88	94·08
$SO_2(OBu^n)_2$	82·6	7·78	7·82	7·85	7·90	94·19
Mean ($>SO_2$)	85·4	7·803	7·838	7·878	7·918	93·59
SO_2Cl_2	78·0	9·67	9·75	9·86	9·97	93·98

TABLE VI.

Values for $>SO$ *from dialkyl sulphites,* $SO(OR)_2$.

Compound.	*P*.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$SO(OMe)_2$	69·4	7·86	7·91	8·02	8·10	72·85
$SO(OEt)_2$	68·7	7·98	8·03	8·14	8·24	73·07
$SO(OPr^n)_2$	67·0	8·07	8·14	8·25	8·34	73·28
$SO(OPr^i)_2$ *	68·3	8·13	8·21	8·32	8·42	72·79
$SO(OBu^n)_2$	65·2	7·99	8·07	8·17	8·26	73·33**
$SO(OBu^i)_2$	66·5	7·99	8·06	8·16	8·26	73·39
$SO(OAm^n)_2$	65·6	8·01	8·07	8·21	8·28	73·23
Mean ($>SO$ excluding *)	67·1	7·983	8·046	8·158	8·247	73·19
$SOCl_2$	64·3	10·31	10·44	10·72	10·82	79·24

** $Mn_D^{20°}$ for $Bu^n_2SO_3$ in VII, **34** should be 278·01 and not 275·07.

$>SO_2 - >SO$ (representing the mean contributions of the additional oxygen atom in passing from dialkyl sulphites to dialkyl sulphates), $>SO - S$ (sulphides; Part XXI, this vol., p. 1820) and $>SO_2 - S$ (sulphides) are tabulated below; these are compared with the constants for the covalent double bonds in ketones, *i.e.*, with $>CO$ (ketones; Part XI, *loc. cit.*) − C (Part IX, *loc. cit.*).

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$>SO_2 - >SO$	18·3	−0·180	−0·208	−0·280	−0·329	20·40
$>SO - S$ (sulphides)	18·5	0·131	0·125	0·077	0·014	20·33
$>SO_2 - S$ (sulphides)	36·8	−0·049	−0·083	−0·203	−0·315	40·73
$>CO$ (ketones) − C	36·5	2·072	2·077	2·122	2·117	16·68

The constants for the $\rangle PO$ grouping were calculated from the relationship $\rangle PO = PO(OR)_3 - 1{\cdot}5\{CH_2(OR)_2 - CH_2\}$. The results, utilising the data of Part VII (*loc. cit.*) upon trialkyl orthophosphates, are in Table VII; the individual variations are somewhat larger than those found for alkyl sulphites and sulphates.

The experimental data required for the calculation of the parachor and the refractivities of phosphorus are scanty: approximate values for the parachor may be obtained from the author's measurements upon phosphorus trichloride and tribromide, and for the refractivities R_C, R_D, and

* Strecker and Spitaler (*Ber.*, 1926, **59**, 1773) have, however, investigated triethyl phosphite.

TABLE VII.

Values for $\geqslant$PO *from trialkyl orthophosphates,* $PO(OR)_3$.

Compound.	*P*.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$PO(OMe)_3$	60·7	5·87 *	5·91	5·94	—	72·05
$PO(OEt)_3$	56·5	5·93	5·95	5·98	6·03	71·63
$PO(OPr^n)_3$	53·3	5·89	5·93	5·96	6·01	72·41
$PO(OPr^i)_3$	50·6	6·03	6·08	6·10	6·16	71·62
$PO(OBu^n)_3$	48·2	6·03	6·07 †	6·09	6·11	72·52
$PO(OBu^i)_3$	49·0	5·72	5·76	5·78	5·82 ‡	72·27
$PO(OAm^n)_3$	—	5·61	5·64	5·68	5·75	72·43
Mean ($\geqslant$PO)	53·1	5·87	5·91	5·93	5·98	72·13
$POCl_3$	60·4	6·98	6·97	7·03	7·12	74·96

* Arithmetical error in VII, **43**; for R_C 27·67, read R_C 27·62.
† Arithmetical error in VII, **47**; for R_D 69·57, read R_D 69·73.
‡ Arithmetical error in VII, **48**; for $R_{G'}$ 70·68, read $R_{G'}$ 70·74.

R_F from the measurements upon three trialkyl phosphines by Jones, Davies, and Dyke (*loc. cit.*). These lead to the following results.

Compound.	*P*.	R_C.	R_D.	R_F.	$R_{G'}$.
PCl_3	36·0	8·62	8·75	8·98	9·19
PBr_3	39·3	—	8·85	—	—
$P(C_3H_7^n)_3$	—	8·93	9·04	9·32	—
$P(C_4H_9^n)_3$	—	8·97	9·07	9·30	—
$P(C_5H_{11}^n)_3$	—	8·82	8·92	9·14	—
Mean (P)	37·7	8·91	9·01	9·25	—

If these constants for phosphorus be subtracted from the mean figures for $\geqslant$PO, the following values for $\geqslant$PO − P are obtained: *P* 15·4; R_C − 3·04; R_D − 3·10; R_F − 3·32. The large negative values for the refractivities are particularly noteworthy.

The constants of the $\geqslant PO_4$ grouping in trialkyl orthophosphates, the $>SO_3$ grouping in dialkyl sulphites, and of the $>SO_4$ grouping in dialkyl sulphates have been computed in the usual manner from the data given in Part VII (*loc. cit.*) by subtracting the values for the alkyl groups (Part XI, *loc. cit.*); the values of the differences $\geqslant PO_4$ − P, $>SO_3$ − S (sulphides) and $>SO_4$ − S (sulphides) are included in Tables VIII, IX, and X respectively for purposes of comparison.

TABLE VIII.

Values for $\geqslant PO_4$ *from trialkyl orthophosphates,* R_3PO_4.

Compound.	*P*.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Me_3PO_4	120·0*	10·71	10·78	10·83	—	141·20
Et_3PO_4	113·8	10·82	10·87	10·94	11·04	139·03
$Pr^n_3PO_4$	109·5	10·73	10·76	10·83	10·91	139·89
$Pr^i_3PO_4$	108·5	10·84	10·86	10·90	10·99	138·36
$Bu^n_3PO_4$	103·4	10·94	10·97	11·03	11·08	140.08
$Bu^i_3PO_4$	103·9	10·63	10·65	10·70	10·77	139·38
$Am^n_3PO_4$	—	10·46	10·49	10·54	10·64	140·21
Mean $\geqslant PO_4$ (excluding *)	107·8	10·733	10·769	10·821	10·905	139·74
$\geqslant PO_4$ − P	70·0	1·82	1·76	1·57	—	—

TABLE IX.

Values for $>SO_3$ *from dialkyl sulphites,* R_2SO_3.

Compound.	*P*.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Me_2SO_3 *	108·9	11·09	11·15	11·28	11·41	118·95
Et_2SO_3	106·9	11·24	11·31	11·44	11·58	118·06
$Pr^n_2SO_3$	104·5	11·30	11·36	11·50	11·61	118·27
$Pr^i_2SO_3$	106·9	11·34	11·40	11·52	11·64	117·28
$Bu^n_2SO_3$	107·0	11·26	11·34	11·46	11·57	118·40
$Bu^i_2SO_3$	103·1	11·26	11·32	11·44	11·56	118·13
$Am^n_2SO_3$	103·1	11·21	11·30	11·45	11·54	118·42
Mean $>SO_3$ (excluding *)	105·3	11·273	11·338	11·468	11·550	118·09
$>SO_3$ − S (sulphides)	56·7	3·421	3·417	3·387	3·317	65·23

TABLE X.

Values for $>SO_4$ *from dialkyl sulphates,* R_2SO_4.

Compound.	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Me_2SO_4	127·1	11·02	11·07	11·13	11·22	138·74
Et_2SO_4	125·7	11·13	11·17	11·24	11·32	138·37
$Pr^n_2SO_4$	121·3	11·00	11·03	11·10	11·15	139·07
$Bu^n_2SO_4$	119·4	11·05	11·09	11·14	11·21	139·26
Mean $>SO_4$	123·4	11·050	11·090	11·153	11·225	138·86
$>SO_4 - S$ (sulphides)	74·8	3·198	3·169	3·072	2·992	86·00

A comparison of the physical constants of the $\geqslant PO$ grouping with those of the $-NO$ grouping (which is generally accepted to contain a covalent double bond) in nitrosoamines has been made. The constants for this grouping are readily determined with the aid of the experimental data for secondary aliphatic amines (Part XXII, preceding paper):

$$-NO = R_2N{\cdot}NO + H - R_2NH$$

The results are given in Table XI, as are also the values of $-NO - N$ (tertiary aliphatic amines) (Part XXII, *loc. cit.*), of O (ethers) (Part XII, *loc. cit.*) + $\overline{|}$ (carbon to carbon) (Part XVI, this vol., p. 658), and of CO (ketones) (Part XI, *loc. cit.*) − C. It will be noted that the differences of the refractivities are positive and of the same order as (O + $\overline{|}$) and (CO − C). [Slightly different vales for (NO − O) are obtained if the constants for N derived from NH_2 (primary aliphatic amines) and NH (secondary aliphatic amines) are employed.] Exact agreement is, indeed, not to be expected as there is no real evidence that the constants for the covalent double bonds are independent of the containing atoms. Sugden, Reed, and Wilkins (*J.*, 1925, **127**, 1525) have stated that the same value is found for the parachor for double bonds between carbon and carbon, carbon and oxygen, carbon and sulphur, and nitrogen and oxygen; this general statement cannot be accepted (see also below) since it has been shown in earlier papers of this series that the parachors (and refractivities) of sulphur, nitrogen, and oxygen vary with the nature of the other atoms attached to these elements.

TABLE XI.

Values of the $-N{=}O$ *grouping from dialkyl nitrosoamines,* $R_2N{\cdot}NO$.

Compound.	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$Et_2N{\cdot}NO$	55·2	5·10	5·16	5·35	5·53	42·91
$Pr^n_2N{\cdot}NO$	54·6	5·17	5·25	5·44	5·63	43·23
$Bu^n_2N{\cdot}NO$	50·4	5·12	5·19	5·40	5·57	43·27
Mean $-N = O$	53·4	5·130	5·200	5·397	5·577	43·14
$-NO - N$ (tertiary aliphatic amines)	46·2	2·432	2·456	2·577	2·663	18·77
O (ethers) + $\overline{|}$ (carbon to carbon)	39·7	3·298	3·339	3·458	3·525	16·67
CO (ketones) − C	35·8	2·007	2·010	2·053	2·047	16·70

The new determination of the refractivities at 20° and the parachors of the dialkyl nitrosoamines have been employed in the computation of the constants of the nitrosamine $-N{\cdot}NO$ grouping; the results are presented in Table XII. The constants for phenyl-methyl-

TABLE XII.

Values for $-N{\cdot}NO$ *from dialkyl nitrosoamines,* $R_2N{\cdot}NO$.

Compound.	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$Me_2N{\cdot}NO$	73·1	7·85	7·96	8·20	8·46	70·12
$Et_2N{\cdot}NO$	69·0	7·73	7·83	8·08	8·35	69·43
$Pr^n_2N{\cdot}NO$	66·9	7·71	7·80	8·06	8·31	69·47
$Bu^n_2N{\cdot}NO$	62·9	7·70	7·81	8·06	8·31	69·44
Mean $-N{\cdot}NO$	68·0	7·748	7·850	8·100	8·358	69·67
NPh(NO)Me	67·8	8·68	8·87	9·48	—	76·90
NPh(NO)Et	66·5	8·66	8·86	9·45	—	75·42

and -ethyl-nitrosoamines (XXII, **528** and XXII, **530**) were derived by subtraction of the figures for methyl- and ethyl-benzene respectively (Part X, this vol., p. 607).

The parachors and refractivities of a number of nitro-paraffins and of alkyl nitrites have been determined, and the constants for the nitro-group and the nitrite group have been computed in the usual manner. The results are collected in Tables XIII and XIV, respectively. In

TABLE XIII.

Values for $-NO_2$ *from nitro-paraffins,* $R{\cdot}NO_2$.

Compound.	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$MeNO_2$	77·2	6·65	6·71	6·82	6·94	65·42
$EtNO_2$	75·6	6·67	6·72	6·84	6·94	65·77
Pr^nNO_2	73·8	6·60	6·67	6·76	6·91	65·61
Pr^iNO_2 *	76·0	6·57	6·61	6·72	6·82	65·28
Bu^nNO_2	72·5	6·70	6·74	6·85	6·95	65·62
Am^nNO_2	71·9	6·67	6·71	6·82	6·92	65·60
$C_6H_{13}{}^nNO_2$	71·6	6·68	6·73	6·85	6·95	65·63
Mean $-NO_2$ (excluding *)	73·8	6·662	6·713	6·823	6·918	65·61
$Ph{\cdot}NO_2$	75·6	7·24	7·36	7·71	8·08	69·10

TABLE XIV.

Values for $-ONO$ *from alkyl nitrites,* $R{\cdot}O{\cdot}NO$.

Compound.	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$Bu^n{\cdot}O{\cdot}NO$	75·6	7·23	7·28	7·42	7·55	62·17
$Am^n{\cdot}O{\cdot}NO$	74·9	7·14	7·19	7·32	7·46	62·30
$C_6H_{13}{}^n{\cdot}O{\cdot}NO$	75·4	7·19	7·24	7·39	7·51	62·34
Mean $-O{\cdot}NO$	75·3	7·187	7·237	7·377	7·507	62·27

comparing the mean constants for the nitro- and the nitrite group, it will be observed that the parachors differ only slightly but the refractivities of the former are appreciably less than those of the latter.

The constants for the nitrate group have been deduced from measurements upon three alkyl nitrates and are given in Table XV. The values for $-NO_3 - -O{\cdot}NO$ (nitrite) and for $-NO_3 - -NO_2$ (nitro) are included in the table; the former differences are of particular interest in that they give the influence of the additional oxygen, presumably attached by a co-ordinate link, in passing from alkyl nitrites to alkyl nitrates. It will be noted that these figures differ considerably from those obtained from alkyl sulphates — alkyl sulphites (Table IV) or $>SO_2 - >SO$.

TABLE XV.

Values for $-NO_3$ *from alkyl nitrates,* RNO_3.

Compound.	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$EtNO_3$	93·8	8·92	8·98	9·12	9·25	87·44
Pr^nNO_3	92·0	9·01	9·06	9·20	9·32	87·65
Bu^nNO_3	92·8	8·99	9·05	9·19	9·31	87·73
Mean $-NO_3$	92·9	8·973	9·030	9·170	9·293	87·59
$-NO_3 - -O{\cdot}NO$ (nitrite)	17·6	1·786	1·793	1·793	1·786	25·32
$-NO_3 - -NO_2$ (nitro)	19·1	2·311	2·327	2·347	2·375	21·98

The parachors and the refractivities of a number of dialkyl carbonates have been determined and the constants of the $>CO_3$ group have been computed in the usual manner. The results are given in Table XVI. The new data may be employed to provide evidence for the usual formula

TABLE XVI.

Values for $-CO_3$ *from dialkyl carbonates,* R_2CO_3.

Compound.	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
Me_2CO_3	85·0	7·62	7·66	7·72	7·80	87·02
Et_2CO_3	83·6	7·67	7·71	7·76	7·84	85·99
$Pr^n{}_2CO_3$	82·3	7·67	7·71	7·78	7·85	86·26
$Bu^n{}_2CO_3$	80·2	7·64	7·67	7·73	7·76	86·35
$Bu^i{}_2CO_3$	80·8	7·71	7·73	7·78	7·84	86·12
Mean $>CO_3$	82·4	7·662	7·696	7·754	7·818	86·35

of dialkyl carbonates $(RO)_2C{=}O$. The constants for the $>CO$ grouping may be calculated by subtraction of the values for $(OR)_2$, which are readily derived from acetals $CH_2(OR)_2 - CH_2$. The constants for $>CO$ thus obtained are in reasonable agreement with those for $>CO$ deduced from dialkyl ketones CORR′ (Part XI, *loc. cit.*).

TABLE XVII.

Values for >CO *from dialkyl carbonates,* $CO(OR)_2$.

Compound.	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$CO(OMe)_2$	45·4	4·39	4·42	4·46	4·49	40·92
$CO(OEt)_2$	45·4	4·41	4·43	4·46	4·50	41·16
$CO(OPr^n)_2$	44·8	4·46	4·49	4·53	4·58	41·27
$CO(OBu^n)_2$	43·4	4·37	4·40	4·44	4·45	41·28
$CO(OBu^i)_2$	44·2	4·44	4·47	4·50	4·54	41·38
Mean >CO	44·6	4·414	4·442	4·478	4·512	41·20
>C=O (ketones)	44·4	4·579	4·601	4·654	4·702	42·41

Determinations of the parachors and refractivities of a number of alkyl thiocyanates and *iso*thiocyanates have been made with the object of deducing the constants of these groups. The results are collected in Tables XVIII and XIX. It is now generally accepted that thiocyanates

TABLE XVIII.

Values for −SCN *from alkyl thiocyanates,* R·SCN.

Compound.	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
MeSCN	113·6	13·18	13·28	13·49	13·68	89·23
EtSCN	112·0	13·33	13·42	13·65	13·82	88·77
Pr^nSCN	111·7	13·34	13·42	13·65	13·84	88·77
Bu^nSCN	110·7	13·39	13·48	13·71	13·89	88·22
Mean −SCN	112·0	13·313	13·400	13·603	13·808	88·90

TABLE XIX.

Values for −NCS *from alkyl* iso*thiocyanates,* R·NCS.

Compound.	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
EtNCS	114·7	15·43	15·62	15·97	16·30	92·37
C_3H_5NCS	113·1	15·46	15·61	15·99	16·30	93·85
Mean −NCS	113·9	15·445	15·615	15·980	16·300	93·11

have the structure R−S−C≡N and *iso*thiocyanates R−N=C=S. Subtraction of the constants for S (in sulphides) (Part XXI, *loc. cit.*) from the mean values for the thiocyanate group −SCN gives the following values for the residual −CN; these are in reasonable agreement with the constants already deduced (Part XVII, *loc. cit.*) for −C≡N for alkyl cyanides.

	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
−CNS − S	63·4	5·461	5·479	5·522	5·575	36·04
−C≡N (Part XVII)	64·6	5·431	5·459	5·513	5·561	36·46

The refractivities and parachors of a number of alkyl xanthates have been determined with the object of deducing the constants for the >C=S grouping. It may be noted that the physical properties (parachor and refractivites) of *ethyl* S-n-*butylxanthate* $CS(OEt)\cdot SBu^n$, n-*butyl* S-*ethylxanthate* $CS(OBu^n)\cdot SEt$ and of *di*-n-*propyl xanthate* are substantially identical. The constants for the >CS grouping were computed from the data for disulphides (Part VII, *loc. cit.*) and acetals (Part XII, *loc. cit.*) thus:

$$>CS = CS(OR)SR - [0{\cdot}5R_2S_2 + 0{\cdot}5\{CH_2(OR)_2 - CH_2\}]$$

The results are summarised in Table XX.

TABLE XX.

Values for >CS *from alkyl xanthates,* CS(OR)·SR.

Compound.	*P.*	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
$CS(OEt)\cdot SEt$	75·8	12·57	12·77	13·35	13·88	77·09
$CS(OPr^n)\cdot SPr^n$	74·6	12·96	13·19	13·80	14·37	77·41
$CS(OBu^n)\cdot SBu^n$	72·3	12·99	13·24	13·86	14·42	77·11
Mean >C=S	74·2	12·84	13·07	13·67	14·22	77·20

The physical constants of the following groups containing covalent double bonds have so far been determined: C=O (Part XI, *loc. cit.*), C=S and N=O; it is of interest to compare the constants for the three different types of double bond with those for the carbon to carbon double bond (Part XVI, this vol., p. 658). As a first approximation, the following values for the atomic constants have been used: C (in CH_2), O (in ethers), S (in sulphides), N (in tertiary aliphatic amines) (*A*) and N (in secondary aliphatic amines) (*B*). Another series of values for the

carbon–sulphur double bond may be computed from Timmermans and Martin's refractivity data (*J. Chim. physique*, **1928**, **25**, 413) (R_C 21·12, R_D 21·39, R_F 22·05, $R_{G'}$ 22·64, and $Mn_D^{20°}$ 123·94) and Lek's parachor (Thesis, Brussels, 1930; Sidgwick, Sugden, and Adams, *B.A. Report*, 1932, p. 265) (143·6) for carbon disulphide. By subtracting the author's constants for C (in CH_2) and S (in sulphides), the following constants are obtained for the carbon–sulphur double bond in carbon disulphide: P 18·9, R_C 1·43, R_D 1·48, R_F 1·65, $R_{G'}$ 1·76, $Mn_D^{20°}$ − 3·75; these, it will be noted, differ considerably from the figures deduced from alkyl xanthates. The main feature of Table XXI is the variation of the constants for the different double bonds; these results do not

TABLE XXI.

Preliminary constants for covalent double bonds.

Nature of bond.	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
C=O	16·0	0·25	0·25	0·27	0·24	−6·04
C=S	17·0	2·42	2·56	2·99	3·33	−1·37
N=O (*A*)	26·4	0·68	0·69	0·79	0·76	−3·97
N=O (*B*)	20·9	0·83	0·85	0·99	1·08	−5·50
C=C	19·9	1·545	1·575	1·672	1·720	−6·07

support Sugden's assertion (*J.*, 1925, **127**, 1525; *op. cit.*, p. 38) that the parachor value is independent of the elements connecting the double bond, although it must be admitted that the variation of the parachor is less than that for the refractivities.

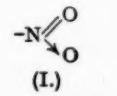
The physical constants of the carbon–nitrogen triple bond may be evaluated by subtraction of C (in CH_2) and N (in tertiary aliphatic amines) from those for nitriles −C≡N (Part XVII, *loc. cit.*); these are compared with those already found for the terminal carbon to carbon triple bond (Part XVII, *loc. cit.*):

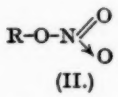
	P.	R_C.	R_D.	R_F.	$R_{G'}$.	$Mn_D^{20°}$.
≡ (carbon–nitrogen)	48·8	0·161	0·124	0·092	−0·008	−13·62
≡ (carbon–carbon, terminal)	40·6	1·959	1·977	2·061	2·084	−12·56

These results are not in agreement with Sugden's statement (*J.*, 1924, **125**, 1179) that the same triple-bond constant [for the parachor] can be used for nitriles and acetylenes (compare Sugden, Reed, and Wilkins, *loc. cit.*).

The parachor and refractivity values for the various elements, structural constants, and groups so far determined are collected in Table XXII; these supersede those of Sugden and of Eisenlohr.

Discussion of the Structure of Esters of Oxy-acids and Related Compounds.—The structures for the nitro-group, alkyl nitrates, thionyl chloride, sulphuryl chloride, dialkyl sulphites, dialkyl sulphates, phosphorus oxychloride, and trialkyl orthophosphates were given as (I)—(VIII) by Sugden, Reed, and Wilkins (*loc. cit.*) from determinations of the parachor and the application of the octet rule:


(I.)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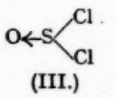
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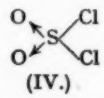
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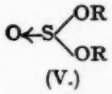
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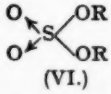
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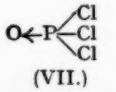
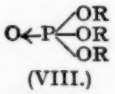
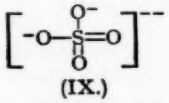

(VII.)


(VIII.)

The presence of co-ordinate or dative links in all these compounds, with the apparent exception of nitro-compounds and of esters of nitric acid, has been questioned on the basis of measurements of bond distances. Thus the S–O distance in the sulphate ion is 1·51 A., which is considerably less than the sum of the single-bond covalent radii (1·70 A.) and approximates to the sum of the double-bond covalent radii (1·49 A.), and has led Pauling ("The Nature of the Chemical Bond", Cornell, 1940, pp. 240—243) to propose the structure (IX) together with such resonating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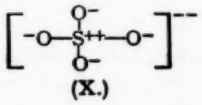
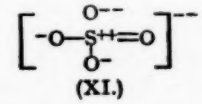

(X.)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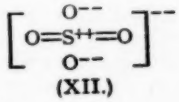
(XII.)

structures as (X)—(XII) to account for the fact that the S–O distance is very close to that expected for pure double bonds. Wells ("Structural Inorganic Chemistry", Oxford, 1945,

TABLE XXII.

Atomic, structural, and group parachors and refractivities.

	P.	R_C.	R_D.	R_F.	R_G.	$Mn_D^{20°}$.
CH_2	40·0	4·624	4·647	4·695	4·735	20·59
H (in CH_2)	15·7	1·026	1·028	1·043	1·040	−2·56
C (in CH_2)	8·6	2·572	2·591	2·601	2·655	25·71
O (in ethers)	19·8	1·753	1·764	1·786	1·805	22·74
O (in acetals)	18·0	1·603	1·607	1·618	1·627	22·41
CO (in ketones)	44·4	4·579	4·601	4·654	4·702	42·41
CO (in methyl ketones)	46·7	4·730	4·758	4·814	4·874	42·42
COO (in esters)	63·4	6·173	6·200	6·261	6·315	64·14
OH (in alcohols)	30·2	2·536	2·546	2·570	2·588	23·94
CO_2H	73·7	7·191	7·226	7·308	7·368	63·98
Cl	55·2	5·821	5·844	5·918	5·973	50·41
Br	68·8	8·681	8·741	8·892	9·011	118·07
I	90·3	13·825	13·954	14·310	14·620	196·27
F	26·1	0·81	0·81	0·79	0·78	21·84
NH_2 (in primary aliphatic amines)	44·0	4·414	4·438	4·507	4·570	22·64
NH (in secondary aliphatic amines)	28·4	3·572	3·610	3·667	3·732	23·34
NH (in secondary aromatic amines)	27·1	4·548	4·678	5·000	5·273	29·52
N (in tertiary aliphatic amines)	7·2	2·698	2·744	2·820	2·914	24·37
N (in tertiary aromatic amines)	?	4·085	4·243	4·675	5·155	30·23
NO (nitroso)	53·4	5·130	5·200	5·397	5·577	43·14
O·NO (nitrite)	75·3	7·187	7·237	7·377	7·507	62·27
NO_2 (nitro)	73·8	6·662	6·713	6·823	6·918	65·61
N·NO (nitrosoamine)	68·0	7·748	7·850	8·100	8·358	69·67
S (in sulphides)	48·6	7·852	7·921	8·081	8·233	52·86
S_2 (in disulphides)	97·2	15·914	16·054	16·410	16·702	106·52
SH (in thiols)	66·4	8·691	8·757	8·919	9·057	50·20
CS (in xanthates)	74·2	12·84	13·07	13·67	14·22	77·20
SCN (in thiocyanates)	112·0	13·313	13·400	13·603	13·808	88·90
NCS (in *iso*thiocyanates)	113·9	15·445	15·615	15·980	16·300	93·11
Carbon–carbon double bond, ═	19·9	1·545	1·575	1·672	1·720	−6·07
Carbon–carbon triple bond, terminal, ≡	40·6	1·959	1·977	2·061	2·084	−12·56
CN (in nitriles)	64·6	5·431	5·459	5·513	5·561	36·46
Three-carbon ring	12·3	0·592	0·614	0·656	0·646	−4·72
Four-carbon ring	10·0	0·303	0·317	0·332	0·322	−4·67
Five-carbon ring	4·6	−0·19	−0·19	−0·19	−0·22	−4·56
Six-carbon ring	1·4	−0·15	−0·15	−0·16	−0·17	−3·53
CO_3 (carbonates)	82·4	7·662	7·696	7·754	7·818	86·35
SO_3 (sulphites)	105·3	11·273	11·338	11·468	11·550	118·09
NO_3 (nitrates)	92·9	8·973	9·030	9·170	9·293	87·59
SO_4 (sulphates)	123·4	11·050	11·090	11·153	11·225	138·86
PO_4 (orthophosphates)	107·8	10·733	10·769	10·821	10·905	139·74
CH_3	55·4	5·636	5·653	5·719	5·746	18·13
C_2H_5	95·4	10·260	10·300	10·414	10·481	38·72
$C_3H_7^n$	135·5	14·895	14·965	15·125	15·235	59·25
$C_3H_7^i$	133·8	14·905	14·975	15·145	15·255	58·95
$C_4H_9^n$	175·3	19·500	19·585	19·800	19·950	79·81
$C_4H_9^i$	173·8	19·530	19·620	19·840	19·990	79·54
$C_4H_9^s$	171·2	19·330	19·420	19·625	19·775	80·21
$C_5H_{11}^n$	215·0	24·140	24·250	24·515	24·700	100·46
$C_5H_{11}^i$ (from the synthetic alcohol)	212·6	24·095	24·195	24·460	24·650	100·30
$C_5H_{11}^i$ (from fermentation alcohol)	213·1	24·170	24·280	24·540	24·720	100·21
$C_6H_{13}^n$	255·0	28·725	28·855	29·160	29·385	121·10
$C_7H_{15}^n$	295·7	33·395	33·550	33·905	34·170	141·75
$C_8H_{17}^n$	335·7	37·960	38·135	38·535	38·830	162·43
C_3H_5 (allyl)	124·3	14·425	14·520	14·745	14·920	57·60
C_6H_5	188·3	25·136	25·359	25·906	26·356	122·03

pp. 320, 321), in discussing Pauling's views on the structure of the sulphate ion, states: "It will probably be felt that this way of arriving at a picture of an ion apparently so simple as SO_4^{--} leaves much to be desired, but it seems the only method available at present. Similar difficulties are experienced with many molecular halides, oxy- and sulpho-halides and the more complex oxy-ions of Si, P, S, and the halogens."

Phillips, Hunter, and Sutton (*loc. cit.*) from considerations of dipole moments, thermal data, and bond distances maintain that the co-ordinate links in the above formulæ (nitrates and nitro-compounds, although formulated, are not discussed in any detail) are double bonds and that such structures as (X)—(XII) are of minor importance. Their arguments are based upon numerous approximations (which are inevitable in the present state of our knowledge) and

include the use of Schomaker and Stevenson's empirical correction for the difference of the Pauling electronegativities between the bonded atoms (*J. Amer. Chem. Soc.*, 1941, **63**, 37) in order to establish their hypothesis that the co-ordinate link is nearly the same length as is to be expected for a normal single covalency between the same two atoms (compare, however, Wells, *op. cit.*, p. 322). It may be noted that the Schomaker and Stevenson correction does not always give the desired result: thus Rogers and Spurr (*J. Amer. Chem. Soc.*, 1947, **69**, 2102) found the Te–Br distance in tellurium dibromide by the electron-diffraction method to be 2·51 A.; the sum of the single bond radii is 2·51 A., and the value obtained after the electronegativity correction has been applied is 2·45 A. A powerful argument employed by Phillips, Hunter, and Sutton is based upon the dipole moments of Me_3NO, Ph_3PO, Ph_3PS, Me_3N,BCl_3, Me_3N,BF_3, Me_3P,BCl_3, Ph_3P,BCl_3, Et_2O,BF_3, and Et_2S,BCl_3. It may be pointed out that many of these compounds are hygroscopic and sparingly soluble in benzene so that the difficulties of measurement are not inconsiderable; furthermore many assumptions are made in deducing the dipole moments of the various links. On the whole it would appear that, although a reasonable case has been made by Phillips, Hunter, and Sutton, the approximations so frequently introduced leave one with the impression that conclusions of such importance require further confirmation with other compounds and by other methods less open to criticism.

Pauling (" General Chemistry ", Freeman, 1947, pp. 161, 162) writes the structures of the oxy-acids (nitric, phosphoric, sulphuric, perchloric, sulphurous, and chlorous acids) on the basis of the octet rule, *i.e.*, with co-ordinate or dative bonds.

The experimental results on parachors and molecular refractivities described in the present communication provide data for the attack of the problem from another viewpoint. It may be said at once that there is no evidence from these two sources that the compounds, previously assumed to contain co-ordinate links, contain double bonds as asserted by Phillips, Hunter, and Sutton. Broadly speaking, the parachor is far less sensitive to changes of structure than the molecular refractivity, so that special consideration will be given to the latter. The evidence may be summarised under the following headings:

(1) The differences (SO_2Cl_2 — $SOCl_2$) and ($POCl_3$ — PCl_3) give values for the parachor approximating to that for the oxygen atom alone (in agreement with Sugden), whilst the molecular refractivites are *negative*. Similar results are obtained for the series (alkyl sulphates — alkyl sulphites), *i.e.*, (R_2SO_4 — R_2SO_3) (Table IV). Data for trialkyl orthophosphites are scanty, but for the triethyl and tri-*n*-amyl esters the R_D differences for R_3PO_4 — R_3PO_3 are negative (— 1·28).

(2) The constants for $>SO_2$ (dialkyl sulphates) and >SO (dialkyl sulphites) have been evaluated (Tables V and VI, respectively). The differences in R_D * for $>SO_2$ — S (sulphides) and for >SO — S (sulphides) are either negative (*P* 36·8; R_D — 0·08) or quite small (*P* 18·5; R_D 0·13).

(3) Similarly the differences in *P* and R_D for $\rangle$PO (orthophosphates; Table VII) — P are 15·3 and — 3·10, respectively.

(4) The constants for the $^-N{=}O$ grouping (*P* 53·4; R_D 5·20; Table XI) may be easily computed from the experimental data on aliphatic nitrosoamines; here the presence of a covalent double bond is generally accepted. The differences in *P* and R_D for $^-N{=}O$ — N (tertiary aliphatic amines) are 46·2 (*i.e.*, O + *double bond*) and 2·56 (a *positive* value considerably greater than for O alone) respectively.

(5) The constants for S=, computed from >C=S deduced from alkyl xanthates (Table XX), are *P* 65·6 and R_D 10·48 † (*i.e.*, >C=S — C); the corresponding values deduced from carbon disulphide are 67·5 and 9·40 respectively. The constants for S (sulphides) are *P* 48·6 and R_D 7·92. It is generally agreed that both alkyl xanthates and carbon disulphide contain covalent double bonds. The corresponding values for (S + " bond attached to oxygen ") calculated from >SO (alkyl sulphites) — O (ethers) are *P* 47·3 and R_D 4·52, whilst for $>SO_2$ (alkyl sulphates) — 2 × O (ethers) the figures are *P* 47·8 and R_D 0·78 respectively. The " bond attached to oxygen " in alkyl sulphites and sulphates would therefore not appear to be a double bond.

* Although R_D is specifically mentioned, the remarks apply equally to R_C, R_F, and $R_{C'}$ throughout the disscussion.

† A higher value (11·29) for the refractivity for S= (D line) is obtained from the ethyl and *n*-propyl dithiothioncarbonate $RO{\cdot}\overset{S}{\overset{\|}{C}}{\cdot}S_2{\cdot}\overset{S}{\overset{\|}{C}}{\cdot}OR$ (Price and Twiss, *J.*, 1912, **51**, 1263; Nasini and Skala, *Gazzetta*, 1887, **17**, 67); this value must be regarded as approximate as it is based upon early measurements of the refractivities.

(6) The constants for the nitro group $-N\begin{matrix}O\\ \searrow\\ O\end{matrix}$ are P 73·8 and R_D 6·71 (Table XIII) and for the nitrite group $-O\cdot N{=}O$ are P 75·3 and R_D 7·24 (Table XIV); the co-ordinate link in nitro-compounds has only a minor effect upon the parachor but produces an appreciable diminution of the molecular refractivity. The contribution of the additional oxygen atom in passing from alkyl nitrites to alkyl nitrates may be calculated from $-NO_3 - -O\cdot N{=}O$ and is P 17·6 and R_D 1·793 [compare $>SO - S$ and $>SO_2 - S$ and also $>PO - P$ in (2) and (3) above].

The following conclusions may be drawn:

(*a*) Parachor and particularly molecular refractivity determinations do not appear to provide any evidence for the presence of double covalent bonds in the compounds (I)—(VIII), which include the simple derivative of the oxy-acids of sulphur and phosphorus.

(*b*) The co-ordinate link in nitro-paraffins and in alkyl nitrates has little effect upon the parachor but there is a distinct decrease in the molecular refractivity.

Calculations are in progress of the bond refractivities and refractivities of electron groups utilising the experimental data described in this and the previous papers of this series; it is hoped that these will help to throw further light on *inter alia* the nature of oxy-bonds.

Structure of the Azide Group.—Sugden (*op. cit.*, p. 123) claims to have shown that the cyclic structure for the azide group is supported by the parachors of a number of covalent azides (Lindemann and Thiele, *Ber.*, 1928, **61**, 1529) and gives a mean value for the azide group of 77·2. In deducing the theoretical value for the cyclic structure he has assumed, without experimental evidence, that the parachor increments for the three-membered nitrogen ring and the nitrogen–nitrogen double bond are identical with those for the corresponding carbon structures; furthermore, the constant for the three-carbon ring is 12·3 (Part XVIII, this vol., p. 1804) and not 16·7 (the figure employed by Sugden). The theoretical parachors for the various alternative structures cannot at present be computed owing to the absence of suitable data for nitrogen compounds. An approximation may, however, be arrived at by comparing the *iso*thiocyanate group $-N{=}C{=}S$ (i) with the azide structure $-N{\rightleftarrows}N{=}N$ (ii). By subtracting the values for C (15·7) and S (48·6) and substituting values for $2 \times N$ (12·0; mean constant deduced from $NH_2 - 2H$ and $NH - H$) in the constant for the *iso*thiocyanate group (113·9), the figure of 73·6 is obtained for the structure (ii). This is sufficiently close to the observed value 77 to support the linear configuration. A similar calculation cannot be made for the molecular refractivity, which is far more sensitive to changes of structure than the parachor. The experimental molecular refractivity data for covalent azides provided by Philip (*J.*, 1908, **93**, 918; 1912, **101**, 1866) cannot at present be employed to decide between the cyclic and the open-chain structures.

Comments on the Work of Strecker and Spitaler (*Ber.*, 1926, **59**, 1755).—This paper was overlooked when the author's experimental work was first planned during 1940 and the literature searched. It is essentially an attempt to deduce the structures of certain inorganic compounds, largely oxy-derivatives of sulphur, by spectrochemical methods; the compounds investigated included the dimethyl, diethyl, and di-*n*-propyl sulphides, sulphones, sulphoxides, symmetrical and unsymmetrical sulphites, and sulphates, and also triethyl phosphite, phosphate, and thiophosphate. Their general discussion is based upon formulæ for sulphoxides, sulphones, *s*-sulphites, *as*-sulphites, and sulphates incorporating covalent double bonds. The refractivity results are similar to those of the present author, and have been interpreted *inter alia* by assigning values for S according to the so-called valency, *e.g.*, for R_{He} they give $C - S^{II} - C$ 7·80, $C - S^{IV} - C$ 6·98, and $C - S^{VI} - C$ 5·34.

Their measurements may be employed to give preliminary values for certain constants by combining them with the experimental data given in this series.

(1) Subtraction of the constants for alkyl groups (Part XI, *loc. cit.*) from the refractivities found for sulphoxides gives $R_2SO - R_2$, *i.e.*, $c - SO - c$.

	R_C.	R_D.	R_F.	R_G.
$Me_2SO - Me_2$	8·64	8·72	8·86	9·05
$Et_2SO - Et_2$	8·53	8·64	8·79	8·98
$Pr^n_2SO - Pr^n_2$	8·52	8·59	8·76	8·92

These constants differ from those found for dialkyl sulphite $o - SO - o$ (Table VI).

(2) The contributions of the oxygen atom in sulphoxide can be deduced directly from $R_2SO - R_2S$ (Part VII, *loc. cit.*) and are:

	R_C.	R_D.	R_F.	$R_{G'}$.
$Me_2SO - Me_2S$	0·89	0·90	0·89	0·93
$Et_2SO - Et_2S$	0·70	0·71	0·67	0·69
$Pr^n{}_2S - Pr^n{}_2S$	0·72	0·73	0·73	0·75

(3) The measurements on the solid dialkyl sulphones were carried out at temperatures of the order of 100° and these values have been employed in the evaluation of the constants for O_2 in sulphones (they are clearly very approximate), *i.e.*, $R_2SO_2 - R_2S$ (Part VII, *loc. cit.*) :

	R_C.	R_D.	R_F.	$R_{G'}$.
$Me_2SO_2 - Me_2S$	8·62	8·66	8·73	8·85
$Et_2SO_2 - Et_2S$	8·58	8·67	8·74	8·86
$Pr^n{}_2SO_2 - Pr^n{}_2S$	8·66	8·68	8·77	8·89

(4) The differences (*as*-dialkyl sulphites — *s*-dialkyl sulphites) are negative. In the results given below the data for dialkyl sulphites are those from Part VII (*loc. cit.*) ; *as*.-diethyl sulphite has already been investigated in Part VII and the figures are given in the line Et (V).

as-Sulphite — *s*-sulphite : R =	R_C.	R_D.	R_F.	$R_{G'}$.
Me	−1·25	−1·27	−1·33	−1·34
Et	−1·42	−1·45	−1·49	−1·49
Et (V)	−1·61	−1·70	−1·70	−1·77
Pr^n	−1·47	−1·50	−1·55	−1·53

Further comments on the above are deferred pending the completion of the calculations of bond refractivities and refractivities of electron groups.

Experimental.

Dichloroacetic Acid.—This acid was prepared from pure chloral hydrate (*Org. Synth.*, 1939, **19**, 38) and had b. p. 105—106°/26—27 mm.

Silver salt. 160 G. of the pure acid were treated with 386 ml. of 3·22N-ammonia solution in a 2-l. beaker, and then a solution of 232 g. of silver nitrate in 500 ml. of water was added with mechanical stirring during 30 minutes. After standing overnight in the dark, the crystalline solid was collected (the filtrate was kept), washed, and dried first between filter paper and finally in a vacuum desiccator over silica gel and anhydrous calcium chloride in the dark to constant weight: the yield of silver dichloroacetate was 148 g. (theory: about 290 g.). The filtrate from the silver salt was treated with excess of dilute hydrochloric acid, filtered, the filtrate extracted three times with ether, dried, and distilled : about 75 g. of dichloroacetic acid were recovered.

Methyl dichloroacetate. 39 G. of silver dichloroacetate were suspended in 75 ml. of sodium-dried A.R. benzene in a flask fitted with a reflux condenser, and 26 g. of pure methyl iodide were added dropwise. The mixture was warmed gently until reaction commenced : when the violent reaction was over, the mixture was refluxed for 2 hours, filtered at the pump, and the solid washed with benzene. The combined filtrate and extracts were washed twice with saturated sodium hydrogen carbonate solution and water, dried ($CaSO_4$), and distilled. The yield of ester, b. p. 143°/763 mm., was 9 g.

Ethyl dichloroacetate. This was prepared from 39 g. of dry silver dichloroacetate, 75 ml. of dry benzene, and 29 g. of pure ethyl iodide. The mixture was refluxed for 5 hours and yielded, as detailed for the methyl ester, 10 g. of ethyl dichloroacetate, b. p. 155·5°/764 mm.

n-*Propyl dichloroacetate.* A mixture of 31 g. of silver dichloroacetate, 75 ml. of dry benzene, and 25 g. of *n*-propyl iodide was refluxed for 1·5 hours, and afforded 11·5 g. of ester, b. p. 174·5—175°/769 mm.

n-*Butyl dichloroacetate.* A mixture of 39 g. of silver dichloroacetate, 75 ml. of dry benzene, and 32 g. of *n*-butyl iodide yielded, as for the methyl ester, after refluxing for 4 hours, 12 g. of *ester*, b. p. 192°/749 mm. (Found : Cl, 38·5. $C_6H_{10}O_2Cl_2$ requires Cl, 38·3%).

Methyl Trichloroacetate.—A mixture of 32 g. of B.D.H. A.R. trichloroacetic acid, 64 g. of Burrough's synthetic absolute methyl alcohol, and 3·2 g. of concentrated sulphuric acid was refluxed for 20 hours, about half of the excess of alcohol was distilled off on a water-bath, the residue poured into excess of water, and the lower layer of ester (24 g.) separated. This was washed with saturated sodium hydrogen carbonate solution and water, dried, and distilled; the ester boiled constantly at 152°/758 mm.

Ethyl Trichloroacetate.—A mixture of 32 g. of the A.R. acid, 92 g. of absolute ethyl alcohol, and 4·6 g. of concentrated sulphuric acid was refluxed for 60 hours and yielded, as for the methyl ester with the modification that the ester was isolated by ether extraction, 20 g. of pure ethyl trichloroacetate, b. p. 166°/755 mm.

n-*Propyl Trichloroacetate.*—A mixture of 32 g. of the A.R. acid, 24 g. of pure *n*-propyl alcohol, 50 ml. of sodium-dried A.R. benzene, and 10 g. of concentrated sulphuric acid was refluxed for 40 hours, poured into excess of water, and ether added to assist the separation of the benzene layer. The ether–benzene extract of the ester was washed with saturated sodium hydrogen carbonate solution and water, dried, and distilled. The yield of ester, b. p. 68°/8·5 mm., was 30 g.

n-*Butyl Trichloroacetate.*—A mixture of 32 g. of the A.R. acid, 30 g. of pure *n*-butyl alcohol, 50 ml. of dry benzene, and 10 g. of concentrated sulphuric acid was refluxed for 60 hours and yielded, as for the *n*-propyl ester, 40 g. of n-*butyl trichloroacetate*, b. p. 204°/762 mm., 81·5°/7·5 mm. (Found : Cl, 48·3. $C_6H_9O_2Cl_3$ requires Cl, 48·5%).

Methylene Chloride.—The commercial product was fractionated and the fraction of b. p. 40—41° was collected. This was washed with 5% sodium carbonate solution and water, dried, and distilled through a Widmer column; b. p. 40°/763 mm.

Methylene Bromide.—This was prepared from commercial 96% bromoform by treatment with alkaline sodium arsenite solution, prepared from A.R. arsenious oxide (*Org. Synth.*, 1929, **9**, 56), and boiled constantly at 97°/760 mm.

Methylene Iodide.—This was prepared by reduction of pure iodoform with alkaline sodium arsenite solution (from A.R. arsenious oxide) (*Org. Synth.*, 1921, **1**, 57). After two distillations, the methylene iodide had b. p. 80°/25 mm. and was straw-coloured. Shaking with a little pure silver powder before distillation reduced the intensity of the colour of the crude product.

Ethylidene Chloride.—A 100-g. sample (Eastman Kodak) was washed with saturated sodium hydrogen carbonate solution until effervescence ceased, then with water, dried, and fractionated; b. p. 57·5°/761 mm.

s-*Tetrachloroethane.*—135 Ml. of the technical product were stirred mechanically for 10 minutes with 17 ml. of concentrated sulphuric acid at 80—90°; the brownish-yellow acid layer was removed, replaced by a further 17 ml. of concentrated sulphuric acid, and the process repeated twice, whereupon the acid appeared unaffected. The acid was separated, and the tetrachloroethane well washed with water and distilled in steam. The organic layer was washed with water, dried (K_2CO_3), and distilled in an all-glass apparatus through a Widmer column; b. p. 147°/770 mm.

Chloroform.—About 100 ml. of A.R. chloroform were shaken with 5 ml. of concentrated sulphuric acid, washed with water until the washings were neutral to litmus, dried ($CaSO_4$), and distilled in an all-glass apparatus through a Widmer column; b. p. 61·5°/765 mm.

Methylchloroform.—The Eastman Kodak product was dried ($CaSO_4$) and distilled in an all-glass apparatus through a Widmer column. All boiled constantly at 73·5°/758 mm.

Carbon Tetrachloride.—The A.R. product was dried ($CaCl_2$) and distilled through a Widmer column; b. p. 76·5°/766 mm.

Ethylidene Bromide.—An Eastman Kodak preparation was washed with sodium hydrogen carbonate solution until effervescence ceased, then with water, dried ($CaCl_2$), and distilled from a Claisen flask with fractionating side arm; b. p. 108°/771 mm. The purified product was colourless, but upon keeping for a few days acquired a pale yellow colour and traces of hydrogen bromide were evolved.

s-*Tetrabromoethane.*—The yellow commercial product (B.D.H.) was shaken three times with 12% of its volume of concentrated sulphuric acid, then washed thrice with water, dried (K_2CO_3, followed by $CaSO_4$), and distilled; b. p. 124°/19 mm., a colourless liquid.

Bromoform.—The B.D.H. product, containing 4% of alcohol, was washed with a saturated solution of calcium chloride to remove the alcohol, dried ($CaCl_2$), and fractionated. Pure bromoform was collected at 148·5°/761 mm. as an almost colourless liquid; this is comparatively unstable and after a day or two a yellow cloudiness is present at the surface.

1 : 2 : 3-*Tribromopropane.*—A large sample, prepared by the interaction of allyl bromide and bromine (*Org. Synth.*, 1925, **5**, 99), was carefully fractionated; b. p. 100°/16 mm.

Triethyl Orthoformate.—A B.D.H. sample was dried ($CaCl_2$) and fractionated through a Widmer column; b. p. 143°/765 mm.

Tri-n-*propyl Orthoformate.*—The Eastman Kodak product was dried and fractionated; b. p. 91°/17 mm.

Tri-n-*butyl Orthoformate.*—The Eastman Kodak product was dried and fractionated; b. p. 127°/16 mm.

Thionyl Chloride.—B.D.H. " redistilled " thionyl chloride was mixed with 10% of its weight of pure quinoline and distilled in an all-glass apparatus through a Widmer column, moisture being carefully excluded; b. p. 76·5°/768 mm.

Sulphuryl Chloride.—B.D.H. " redistilled " sulphuryl chloride was distilled in an all-glass apparatus through a Widmer column, entrance of moisture being prevented; b. p. 69·5°/775 mm.

Phosphorus Trichloride.—A pure commercial product was fractionally distilled as for sulphuryl chloride; b. p. 75°/772 mm.

Phosphorus Oxychloride.—The B.D.H. pure product was fractionally distilled as for sulphuryl chloride; b. p. 106·5°/775 mm.

Phosphorus Tribromide.—In a 500-ml. three-necked flask, equipped with a dropping funnel, reflux condenser, and carbon tetrachloride-sealed mechanical stirrer, were placed 28 g. of dry purified red phosphorus and 200 ml. of dry A.R. carbon tetrachloride: ground glass joints are to be preferred, but " neoprene " or used rubber stoppers may also be used. The mixture was vigorously stirred and 198 g. of A.R. bromine were added during 1·5—2 hours. The reaction mixture was gently refluxed on a water-bath for 15 minutes, allowed to settle, and the clear solution filtered through a fluted filter paper into the 500-ml. flask of an all-glass distillation apparatus, which included a well-lagged, all-glass 15 cm. Dufton column. The solvent was distilled off on a water-bath; upon rise of the temperature, the phosphorus tribromide (190 g.) passed over at 168—169°/765 mm. Upon redistillation from an all-glass apparatus, without a column, the product boiled constantly at 171·5°/763 mm.

Dimethylnitrosoamine.—This was prepared from pure dimethylamine hydrochloride and nitrous acid (compare Cohen, " Practical Organic Chemistry ", 1924, p. 96) and boiled constantly at 151°/767 mm.

Diethylnitrosoamine.—36·5 G. of pure diethylamine were added slowly to the calculated quantity of 5N-hydrochloric acid contained in a 250-ml. distilling flask, followed by 39 g. of sodium nitrite (assumed of 90% purity). The contents of the flask were rapidly distilled to dryness. The upper yellow layer of the distillate was removed, and the lower layer was saturated with A.R. potassium carbonate whereupon more of the nitrosoamine separated and was added to the upper layer. The crude nitrosoamine was dried (K_2CO_3) during 24 hours and distilled. The yield of diethylnitrosoamine, b. p. 174·5°/777 mm., was 44 g.

Di-n-*propylnitrosoamine.*—This was prepared from 29 g. of di-*n*-propylamine (Eastman Kodak), 58 ml. of 5N-hydrochloric acid, and 22 g. of sodium nitrite, as for the diethyl compound. The yield of product, b. p. 89°/13 mm., was 31 g. (compare Schmidt, *Z. physikal. Chem.*, 1907, **58**, 513).

Di-n-*butylnitrosoamine.*—26 G. of Sharples's di-*n*-butylamine were added to 41 ml. of 5N-hydrochloric acid; some hydrochloride separated out and the mixture was transferred with the aid of 20 ml. of water

to a 200-ml. distilling flask containing 15·5 g. of sodium nitrite (assumed of 90% purity). Upon warming, an upper layer appeared; the mixture was rapidly distilled to dryness, and the nitrosoamine isolated as for the diethyl analogue. The yield was 26 g.; b. p. 125—125·5°/21 mm.

Nitromethane.—About 150 g. of highly purified nitromethane, kindly supplied by Imperial Chemical Industries Ltd., were dried ($CaSO_4$) and distilled through a three-section Pyrex Young and Thomas column. Most of it passed over at 101°/762 mm.

Nitroethane.—A highly purified sample, presented by Imperial Chemical Industries Ltd., was dried and distilled as for nitromethane; b. p. 130·5°/761 mm.

2-*Nitro*-n-*propane.*—The I.C.I. product was purified as for nitromethane; b. p. 119·5°/752 mm.

1-*Nitro*-n-*butane.*—Commercially pure silver nitrite (Johnson and Matthey) was washed with absolute alcohol and then with sodium-dried ether, and dried by heating at 100° for 20 minutes, followed by keeping in a vacuum desiccator for 24 hours. In a 200-ml. distilling flask, fitted with a reflux condenser and with the side arm closed by a cork, were placed 64 g. of dry *n*-butyl bromide and 80 g. of the purified silver nitrite. No reaction occurred in the cold. After standing for 2 hours, the mixture was heated successively on a steam-bath for 4 hours (some brown fumes were evolved) and in an oil-bath at 110° for 8 hours. The mixture was distilled and the fraction, b. p. 150—151·5°/780 mm. (18 g.), was collected separately. This was dried ($CaSO_4$) and distilled: pure 1-nitro-*n*-butane was collected at 151·5—152·5°/780 mm., as a colourless liquid.

1-*Nitro*-n-*pentane.*—A mixture of 56 g. of dry silver nitrite and 50 g. of *n*-amyl bromide was heated, as for 1-nitro-*n*-butane, in a bath at 110° for 2 hours, at 115—125° for 2·5 hours, kept at room temperature for 12 hours, and then at 120—130° for 2·5 hours. Distillation yielded 15 g. of a fraction, b. p. 170—173°/775 mm., which was yellow. Redistillation gave pure 1-nitro-*n*-pentane, b. p. 66°/16 mm., as a colourless liquid. Distillation at atmospheric pressure yields a yellow product, evidently due to slight decomposition.

1-*Nitro*-n-*hexane.*—A mixture of 41 g. of dry silver nitrite, 51 g. of *n*-hexyl iodide, and 100 ml. of sodium-dried ether was refluxed for 8 hours, the ethereal solution was decanted, and the solid thoroughly washed with dry ether. After removal of the ether, the residue was distilled and the following fractions were collected, all of which were colourless: 100—160°, 9 g.; 160—189°, 4·5 g.; 190—193°, 13 g. The last fraction was dried ($CaSO_4$) and distilled; b. p. 81·5°/15 mm. The silver nitrite–*n*-hexyl bromide procedure was less satisfactory.

n-*Butyl Nitrite.*—This was prepared from *n*-butyl alcohol and nitrous acid (*Org. Synth.*, 1936, **16**, 7) and was collected as a pale yellow liquid, b. p. 27°/88 mm. The physical measurements for all alkyl nitrites were carried out immediately after distillation because of their comparative instability.

n-*Amyl Nitrite.*—A solution of 95 g. of sodium nitrite in 375 ml. of water was placed in a 1-l. three-necked flask, equipped with a mechanical stirrer, a thermometer, and a dropping funnel with stem extending to the bottom of the flask, and cooled to 0°. A mixture of 25 ml. of water, 62·5 g. of concentrated sulphuric acid, and 110 g. of redistilled *n*-amyl alcohol (Sharples, b. p. 137°/766 mm.), cooled to 0°, was added with stirring during 1 hour; the temperature was maintained at ± 1° throughout. After standing at 0° for 1·5 hours, the mixture was filtered, the yellow amyl nitrite layer was separated and washed twice with 25 ml. portions of a solution containing 1 g. of sodium hydrogen carbonate and 12·5 g. of sodium chloride in 50 ml. of water, and then dried ($CaSO_4$). The crude nitrite (107 g.) upon distillation passed over largely at 104—105°/763 mm.; a middle fraction, b. p. 104·5°/763 mm., had $d_4^{20°}$ 0·8816, $n_D^{20°}$ 1·3892. The compound was distilled under reduced pressure for the physical measurements; b. p. 29°/40 mm.

n-*Hexyl Nitrite.*—This was prepared similarly to *n*-amyl nitrite with the substitution of 127·5 g. of *n*-hexyl alcohol (Carbon and Carbide Corporation, b. p. 156—157°/752 mm.) for the *n*-amyl alcohol. The yield of crude nitrite was 125 g.; this boiled at 129—130°/761 mm. and a middle fraction, immediately after distillation, had $d_4^{20°}$ 0·8810, $n_D^{20°}$ 1·3986, and after 24 hours $d_4^{20°}$ 0·8810, $n_D^{20°}$ 1·3992. The systematic physical measurements were carried out with a sample which was distilled under reduced pressure; b. p. 52°/44 mm.

Nitrobenzene.—The A.R. product (B.D.H.) was distilled from an all-glass apparatus and a middle fraction was collected; b. p. 207·5°/760 mm.

Ethyl Nitrate.—An Eastman Kodak preparation was washed twice with water, dried ($MgSO_4$) and distilled through a fractionating column in an all-glass apparatus; b. p. 88°/757 mm.

n-*Propyl Nitrate.*—100 G. of pure concentrated nitric acid were boiled with 2 g. of urea until effervescence ceased (20 minutes) and then cooled to 0°. A solution of 12·5 g. of urea in 60 g. of pure *n*-propyl alcohol, cooled to 0°, was introduced during 15 minutes, allowed to stand for 15 minutes, and then distilled in an all-glass apparatus from a bath at 110—115°. The distillate (100 ml.) was well washed with brine (a few drops of sodium hydroxide solution were added to the final wash solution to remove the last traces of acid), then washed with water and dried ($MgSO_4$). Fractional distillation through an all-glass apparatus from an oil-bath yielded 30 ml. of *n*-propyl alcohol (b. p. 95—105°, mainly 95—97°), followed by 25 g. of *n*-propyl nitrate at 109—110°. Refractionation of the *n*-propyl nitrate gave the pure compound, b. p. 110°/762 mm.

n-*Butyl Nitrate.*—This was prepared from 100 g. of nitrous acid-free nitric acid and 74 g. of pure *n*-butyl alcohol as described for *n*-propyl nitrate. The yield of *n*-butyl nitrate, b. p. 135—135·5°/762 mm., was 24 g.

Dimethyl Carbonate.—100 G. of the commercial product (B.D.H.) were washed successively with 10% sodium carbonate solution, saturated calcium chloride solution, and water, dried by shaking mechanically for 1 hour with anhydrous calcium chloride (compare *Org. Synth.*, 1931, **11**, 99, Note 3), and fractionated; b. p. 89·5°/755 mm.

Diethyl carbonate (Hopkin and Williams), di-*n*-propyl carbonate (Eastman Kodak), di-*n*-butyl carbonate (Eastman Kodak) and di*iso*butyl carbonate (Eastman Kodak) were similarly purified and had b. p. 125·5°/758 mm., 165°/752 mm., 204·5°/758 mm., and 187·5°/763 mm., respectively.

Methyl Thiocyanate.—The Eastman Kodak product was dried ($CaSO_4$) and fractionated; b. p. 130·5°/765 mm.

Ethyl Thiocyanate.—The Eastman Kodak product was dried (Na_2SO_4) and fractionated; b. p. 145·5°/765 mm.

n-*Propyl Thiocyanate.*—In a 1-l. three-necked flask, fitted with a dropping funnel, a mercury-sealed mechanical stirrer, and a reflux condenser, was placed a mixture of 133 g. of A.R. potassium thiocyanate and 312 g. of rectified spirit. The stirrer was set in motion, the mixture heated on a ring burner, and 154 g. of *n*-propyl bromide added during 20 minutes; potassium bromide separated and the mixture was refluxed for 5 hours with vigorous stirring in order to avoid bumping. After the mixture had been kept overnight, the potassium bromide were filtered off and washed with 75 ml. of rectified spirit. The combined filtrate and washings were distilled on a water-bath through a four-section Pyrex Young and Thomas column to separate most of the alcohol. The residue was treated with 125 ml. of water, the upper layer separated, and the aqueous phase extracted with two 50-ml. portions of ether. The combined upper layer and ether extracts were dried and distilled from a 250-ml. flask through a well-lagged three-section Pyrex Young and Thomas column. After the ether and a little alcohol had passed over at 78°, the temperature rose sharply to 164·5—165°/762 mm. and 93 g. passed over at this temperature. Upon redistillation, the *n*-propyl thiocyanate boiled constantly at 164·5°/760 mm. The above procedure is superior to that described in *Org. Synth.*, 1931, **11**, 92, for *iso*propyl thiocyanate since it gives a pure product (b. p. range <1°) in one operation.

n-*Butyl Thiocyanate.*—This was prepared, as for the *n*-propyl compound, from 133 g. of A.R. potassium thocyanate, 312 g. of rectified spirit, and 172 g. of *n*-butyl bromide. The yield of crude ester, b. p. 183°, was 126 g. This was further dried ($CaSO_4$) and redistilled; b. p. 184°/770 mm.

Ethyl iso*Thiocyanate.*—The Eastman Kodak product was dried (Na_2SO_4) and distilled from a Claisen flask with fractionating side arm; b. p. 132—132·5°/762 mm.

Allyl iso*Thiocyanate.*—The B.D.H. pure product was fractionated as for the ethyl compound; b. p. 151—151·5°/768 mm.

Potassium Ethyl Xanthate.—42 G. of potassium hydroxide pellets were dissolved in 120 g. of absolute ethyl alcohol (refluxing was necessary) and the cold solution decanted from the undissolved impurities. 57 G. of A.R. carbon disulphide were added slowly and with constant shaking; the mixture set almost solid. The solid was filtered off and washed twice with ether (*d* 0·720) and once with anhydrous ether; the yield was 110 g. The ester was dried by leaving it for 3 days in a vacuum desiccator over silica gel; the yield of the dry compound was 74 g.

Diethyl Xanthate.—A mixture of 32 g. of potassium ethyl xanthate, 50 ml. of absolute ethyl alcohol, and 32 g. of ethyl iodide was refluxed for 3 hours: no reaction occurred in the cold but within 15 minutes of heating the yellow mixture became white owing to separation of potassium iodide. Excess of water was added, and the lower layer separated, washed with water and dried ($CaSO_4$). The crude dry compound (29·5 g.) had b. p. 196—198°/761 mm. This was redistilled for the physical measurements; b. p. 70·2°/4·9 mm.

Di-n-*propyl Xanthate.*—A mixture of 42 g. of potassium *n*-propyl xanthate, 50 ml. of absolute alcohol, and 41·5 g. of *n*-propyl iodide was warmed gently on a water-bath until reaction commenced; after 1 hour the vigorous reaction subsided and the mixture was refluxed for 3 hours. The crude *ester* (36 g.) was isolated as for the ethyl compound and had b. p. 91·1°/4·5 mm. (Found: S, 35·9. $C_7H_{14}OS_2$ requires S, 36·0%).

Potassium n-*Propyl Xanthate.*—28 G. of potassium hydroxide pellets were refluxed with 100 g. of *n*-propyl alcohol for 2 hours, and then cooled to room temperature. The solution was decanted from the little solid which had separated, and 38 g. of A.R. carbon disulphide were added slowly. After cooling in ice, the solid was filtered off, washed twice with ether (*d* 0·720) and once with anhydrous ether, and dried over silica gel in a vacuum desiccator to constant weight. The yield of dry xanthate was 42 g.

Ethyl S-n-*Butylxanthate.*—This was prepared from 32 g. of potassium ethyl xanthate, 50 ml. of absolute alcohol, and 37 g. of *n*-butyl iodide as detailed for diethyl xanthate and the product was isolated directly after saturation of the diluted reaction mixture with salt. The crude dry *xanthate* weighed 35 g., and on distillation boiled constantly at 90·3°/4·0 mm. (Found: S, 35·8. $C_7H_{14}OS_2$ requires S, 36·0%).

Potassium n-*Butyl Xanthate.*—20 G. of potassium hydroxide pellets were refluxed with 100 g. of *n*-butyl alcohol until dissolved and then allowed to cool to room temperature. The solution was decanted from the impurities and the little solid potassium hydroxide which had separated, and then 36 g. of A.R. carbon disulphide were slowly added. After cooling in ice, the potassium derivative was filtered off, washed successively with ether (*d* 0·720) and sodium-dried ether, and dried in a vacuum desiccator over silica gel and anhydrous calcium chloride for 3 days. The yield of dry potassium *n*-butyl xanthate was 42 g. It crystallises well from absolute ethyl alcohol.

n-*Butyl* S-*Ethylxanthate.*—The crude product, prepared from 47 g. of potassium *n*-butyl xanthate, 50 ml. of absolute ethyl alcohol, and 39 g. of ethyl iodide as detailed for ethyl *S*-*n*-butylxanthate, weighed 42 g. The pure *ester* boiled at 91·0°/4·3 mm. (Found: S, 35·0. $C_7H_{14}OS_2$ requires S, 36·0%).

Di-n-*butyl Xanthate.*—This was prepared in the usual manner from 31·5 g. of potassium *n*-butyl xanthate, 50 ml. of absolute ethyl alcohol, and 30 g. of *n*-butyl iodide. The yield of *xanthate*, b. p. 117·0°/4·0 mm., was 29 g. (Found: S, 31·3. $C_9H_{18}OS_2$ requires S, 31·1%).

545. *Methyl dichloroacetate.* B. p. 143°/763 mm.; *M* 142·95; n_C 1·44034, n_D 1·44275, n_F 1·44864, $n_{G'}$ 1·45302; R_C 27·38, R_D 27·52, R_F 27·83, $R_{G'}$ 28·07; $Mn_D^{20°}$ 206·25. Densities determined: $d_4^{20°}$ 1·3767, $d_4^{41·2°}$ 1·3481, $d_4^{60·4°}$ 1·3221, $d_4^{85·0°}$ 1·2858. Apparatus *D*.

(These headings apply to all the succeeding tables in this paper).

t.	*H.*	$d_4^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_4^{t°}$.	*γ.*	*P.*
18·0°	10·24	1·3784	34·86	252·0	60·8°	9·06	1·3216	29·57	252·2
21·0	10·13	1·3753	34·41	251·7	86·3	8·35	1·2840	26·48	252·6
41·4	9·60	1·3478	31·95	252·2				Mean	252·1

546. *Ethyl dichloroacetate.* B. p. 155·5°/764 mm.; M 157·00; n_C 1·43608, n_D 1·43841, n_F 1·44220, $n_{G'}$ 1·44853; R_C 32·01, R_D 32·16, R_F 32·53, $R_{G'}$ 32·80; $Mn_D^{20°}$ 225·83. Densities determined: $d_{4°}^{20°}$ 1·2826, $d_{4°}^{41·3°}$ 1·2553, $d_{4°}^{61·4°}$ 1·2298, $d_{4°}^{86·6°}$ 1·1959. Apparatus *D*.

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
19·9°	10·36	1·2827	32·74	292·9	61·4°	9·09	1·2298	27·61	292·6
27·2	10·07	1·2733	31·67	292·5	87·4	8·43	1·1949	24·88	293·4
41·6	9·70	1·2549	30·06	293·0				Mean	292·9

547. n-*Propyl dichloroacetate.* B. p. 174·5—175°/769 mm.; M 171·02; n_C 1·43759, n_D 1·43993, n_F 1·44572, $n_{G'}$ 1·45000; R_C 36·68, R_F 36·85, R_F 37·27, $R_{G'}$ 37·58; $Mn_D^{20°}$ 246·25. Densities determined: $d_{4°}^{20°}$ 1·2230, $d_{4°}^{41·5°}$ 1·1975, $d_{4°}^{60·9°}$ 1·1740, $d_{4°}^{86·6°}$ 1·1425. Apparatus *A*.

16·5°	13·52	1·2272	31·07	329·0	41·2°	12·64	1·1979	28·35	329·4
21·4	13·41	1·2213	30·67	329·5	61·9	11·95	1·1728	26·24	330·0
29·9	13·12	1·2111	29·75	329·8	86·3	11·06	1·1429	23·67	330·7
								Mean	329·6

548. n-*Butyl dichloroacetate.* B. p. 192°/749 mm.; M 185·05; n_C 1·44009, n_D 1·44245, n_F 1·44823, $n_{G'}$ 1·45249; R_C 41·21, R_D 41·40, R_F 41·86, $R_{G'}$ 42·21; $Mn_D^{20°}$ 266·93. Densities determined: $d_{4°}^{20°}$ 1·1848, $d_{4°}^{41·5°}$ 1·1600, $d_{4°}^{60·9°}$ 1·1384, $d_{4°}^{85·6°}$ 1·1102. Apparatus *D*.

19·8°	10·46	1·1850	30·61	367·3	60·9°	9·36	1·1384	26·31	368·2
27·5	10·24	1·1764	29·75	367·4	86·7	8·74	1·1090	23·94	369·0
41·6	9·86	1·1599	28·24	367·8				Mean	367·9

549. *Methyl trichloroacetate.* B. p. 152°/758 mm.; M 177·43; n_C 1·45448, n_D 1·45707, n_F 1·46337, $n_{G'}$ 1·46808; R_C 32·31, R_D 32·47, R_F 32·86, $R_{G'}$ 33·14; $Mn_D^{20°}$ 258·53. Densities determined: $d_{4°}^{20°}$ 1·4884, $d_{4°}^{41·6°}$ 1·4564, $d_{4°}^{60·1°}$ 1·4290, $d_{4°}^{85·7°}$ 1·3901. Apparatus *A*.

13·3°	12·09	1·4984	33·92	285·8	61·2°	10·53	1·4274	28·14	286·3
18·3	11·95	1·4909	33·36	286·0	86·3	9·74	1·3892	25·34	286·5
41·5	11·22	1·4565	30·60	286·5				Mean	286·2

550. *Ethyl trichloroacetate.* B. p. 166°/755; M 191·46; n_C 1·44747, n_D 1·44997, n_F 1·45608, $n_{G'}$ 1·46059; R_C 37·11, R_D 37·28, R_F 37·72, $R_{G'}$ 38·04; $Mn_D^{20°}$ 277·62. Densities determined: $d_{4°}^{20°}$ 1·3800, $d_{4°}^{41·2°}$ 1·3512, $d_{4°}^{59·4°}$ 1·3266, $d_{4°}^{85·5°}$ 1·2883. Apparatus *D*.

15·3°	9·16	1·3864	31·36	326·8	41·4°	8·52	1·3509	28·42	327·2
18·9	9·08	1·3815	30·98	327·0	60·8	8·04	1·3247	26·30	327·2
23·1	9·00	1·3757	30·58	327·1	86·5	7·48	1·2883	23·80	328·2
								Mean	327·3

551. n-*Propyl trichloroacetate.* B. p. 68°/8·5 mm.; M 205·49; n_C 1·44810, n_D 1·45057, n_F 1·45666, $n_{G'}$ 1·46113; R_C 41·60, R_D 41·80, R_F 42·29, $R_{G'}$ 42·64; $Mn_D^{20°}$ 298·08. Densities determined: $d_{4°}^{20°}$ 1·3225, $d_{4°}^{41·9°}$ 1·2936, $d_{4°}^{61·7°}$ 1·2685, $d_{4°}^{85·6°}$ 1·2385. Apparatus *A*.

17·9°	12·39	1·3252	30·75	365·1	42·0°	11·54	1·2935	27·95	365·3
21·5	12·25	1·3205	30·29	365·1	62·9	10·88	1·2669	25·81	365·6
25·8	12·12	1·3150	29·84	365·2	87·8	10·08	1·2356	23·32	365·5
								Mean	365·3

552. n-*Butyl trichloroacetate.* B. p. 81·5°/7·5 mm.; M 219·51; n_C 1·44941, n_D 1·45187, n_F 1·45792, $n_{G'}$ 1·46250; R_C 46·23, R_D 46·45, R_F 46·98, $R_{G'}$ 47·39; $Mn_D^{20°}$ 318·70. Densities determined: $d_{4°}^{20°}$ 1·2747, $d_{4°}^{40·1°}$ 1·2505, $d_{4°}^{59·8°}$ 1·2278, $d_{4°}^{84·8°}$ 1·1979. Apparatus *A*.

13·3°	12·85	1·2827	30·79	403·4	40·8°	12·06	1·2497	28·22	404·8
17·1	12·74	1·2782	30·49	403·6	61·1	11·37	1·2259	26·10	404·7
22·8	12·62	1·2720	30·06	404·1	86·9	10·56	1·1954	23·64	404·9
								Mean	404·3

553. *Methylene chloride.* B. p. 40°/763 mm.; M 84·95; n_C 1·42214, n_D 1·42456, n_F 1·43034, $n_{G'}$ 1·43470; R_C 16·30, R_D 16·38, R_F 16·58, $R_{G'}$ 16·72; $Mn_D^{20°}$ 120·80. Densities determined: $d_{4°}^{20°}$ 1·3247, $d_{4°}^{25·0°}$ 1·3169. Apparatus *A*.

19·3°	11·27	1·3258	27·98	147·5	26·9°	10·97	1·3139	26·99	147·6
23·3	11·07	1·3195	27·35	147·4				Mean	147·5

554. *Methylene bromide.* B. p. 97°/760 mm.; M 173·86; n_C 1·53707, n_D 1·54119, n_F 1·55177, $n_{G'}$ 1·55996; R_C 21·76, R_D 21·90, R_F 22·25; $R_{G'}$ 22·53; $Mn_D^{20°}$ 267·95. Densities determined: $d_{4°}^{20°}$ 2·4956, $d_{4°}^{42·6°}$ 2·4405, $d_{4°}^{61·6°}$ 2·3911, $d_{4°}^{84·1°}$ 2·3266. Apparatus *A*.

18·4°	8·55	2·4997	40·02	174·9	60·5°	7·50	2·3939	33·61	175·0
41·0	8·04	2·4430	36·78	175·3	85·4	6·91	2·3284	30·13	175·2
								Mean	175·1

555. *Methylene iodide.* B. p. 80°/25 mm.; *M* 267·87. Densities determined: $d_{4°}^{20°}$ 3·3240, $d_{4°}^{41·3°}$ 3·2692, $d_{4°}^{60·9°}$ 3·2204, $d_{4°}^{86·3°}$ 3·1550. The results for the surface-tension measurements were unsatisfactory and the refractive indices were outside the range of the prisms available for the Pulfrich refractometer. The $d_{4°}^{20°}$ value was in good agreement with the figure interpolated from the results of Timmermans and Hennaut-Roland (*J. Chim. physique*, 1932, **29**, 529); their values for the refractive indices, interpolated to 20°, are n_C 1·73098, n_D 1·74108, n_F 1·76826 and give R_C 32·20, R_D 32·54, R_F 33·43, $Mn_D^{20°}$ 466·39.

556. *Ethylidene chloride.* B. p. 57·5°/761 mm.; *M* 98·97; n_C 1·41369, n_D 1·41596, n_F 1·42157, $n_{G'}$ 1·42572; R_C 20·99, R_D 21·09, R_F 21·34, $R_{G'}$ 21·52; $Mn_D^{20°}$ 140·14. Densities determined: $d_{4°}^{20°}$ 1·1776, $d_{4°}^{41·4°}$ 1·1535. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
17·1°	11·33	1·1809	25·05	187·6	41·1°	10·26	1·1538	22·17	187·9
23·3	11·01	1·1739	24·20	187·3				Mean	187·6

557. s-*Tetrachloroethane.* B. p. 147°/770 mm.; *M* 167·88; n_C 1·49165, n_D 1·49437, n_F 1·50128, $n_{G'}$ 1·50645; R_C 30·46, R_D 30·60, R_F 30·96, $R_{G'}$ 31·23; $Mn_D^{20°}$ 250·88. Densities determined: $d_{4°}^{20°}$ 1·5984, $d_{4°}^{42·3°}$ 1·5640, $d_{4°}^{61·6°}$ 1·5349, $d_{4°}^{87·6°}$ 1·4954. Apparatus *A*.

17·2°	12·21	1·6027	36·64	257·7	60·3°	10·75	1·5369	30·91	257·6
20·9	12·09	1·5970	36·15	257·8	86·2	9·97	1·4975	27·96	257·8
40·4	11·43	1·5669	33·54	257·8				Mean	257·7

558. *Chloroform.* B. p. 61·5°/765 mm.; *M* 119·40; n_C 1·44353, n_D 1·44611, n_F 1·45232, $n_{G'}$ 1·45700; R_C 21·26, R_D 21·37, R_F 21·63, $R_{G'}$ 21·82; $Mn_D^{20°}$ 172·66. Densities determined: $d_{4°}^{20°}$ 1·4904, $d_{4°}^{49·3°}$ 1·4521. Apparatus *A*.

15·3°	9·93	1·4993	27·88	183·0	26·2°	9·62	1·4787	26·64	183·4
17·5	9·87	1·4951	27·63	183·1	40·1	9·07	1·4525	24·67	183·4
								Mean	183·2

559. *Methylchloroform.* B. p. 73·5°/758 mm.; *M* 133·42; n_C 1·43574, n_D 1·43832, n_F 1·44433, $n_{G'}$ 1·44851; R_C 26·06, R_D 26·20, R_F 26·51, $R_{G'}$ 26·73; $Mn_D^{20°}$ 191·90. Densities determined: $d_{4°}^{20°}$ 1·3376, $d_{4°}^{40·8°}$ 1·3031, $d_{4°}^{62·3°}$ 1·2684. Apparatus *E*.

21·0°	8·25	1·3360	25·67	224·8	40·9°	7·60	1·3029	23·06	224·8
28·3	8·03	1·3239	24·76	224·8	60·6	7·00	1·2712	20·72	224·5
								Mean	224·7

560. *Carbon tetrachloride.* B. p. 76·5°/766 mm.; *M* 153·84; n_C 1·45763, n_D 1·46025, n_F 1·46706, $n_{G'}$ 1·47194; R_C 26·31, R_D 26·45, R_F 26·86, $R_{G'}$ 27·08; $Mn_D^{20°}$ 224·65. Densities determined: $d_{4°}^{20°}$ 1·5941, $d_{4°}^{40·8°}$ 1·5551, $d_{4°}^{57·8°}$ 1·5228. Apparatus *A*.

20·1°	9·25	1·5939	27·61	221·2	40·8°	8·44	1·5551	24·58	220·5
24·9	9·16	1·5848	27·18	221·1	59·5	7·92	1·5196	22·54	221·0
								Mean	221·0

561. *Ethylidene bromide.* B. p. 108°/771 mm.; *M* 187·89; n_C 1·50849, n_D 1·51223, n_F 1·52167, $n_{G'}$ 1·52917; R_C 26·67, R_D 26·63, R_F 27·25, $R_{G'}$ 27·58; $Mn_D^{20°}$ 284·13. Densities determined: $d_{4°}^{20°}$ 2·1018, $d_{4°}^{42·4°}$ 2·0540, $d_{4°}^{60·0°}$ 2·0129. Apparatus *A*.

16·3°	8·64	2·1100	34·14	215·2	62·4°	7·49	2·0076	28·16	215·6
41·2	8·04	2·0562	30·96	215·5				Mean	215·4

562. s-*Tetrabromoethane.* B. p. 124°/19 mm.; *M* 345·70; n_C 1·63011, n_D 1·63533, n_F 1·64847; R_C 41·70, R_D 41·97, R_F 42·66; $Mn_D^{20°}$ 565·32. Densities determined: $d_{4°}^{20°}$ 2·9501, $d_{4°}^{42·0°}$ 2·9036, $d_{4°}^{61·1°}$ 2·8625, $d_{4°}^{87·5°}$ 2·8066. The results of the surface-tension measurements by the capillary rise method were not entirely satisfactory; it is hoped to repeat them by the method of maximum bubble pressure.

563. *Bromoform.* B. p. 148·5°/761 mm.; *M* 252·77; n_C 1·59256, n_D 1·59763, n_F 1·61059, $n_{G'}$ 1·62084; R_C 29·65, R_D 29·86, R_F 30·38, $R_{G'}$ 30·79; $Mn_D^{20°}$ 403·83. Densities determined: $d_{4°}^{20°}$ 2·8870, $d_{4°}^{40·0°}$ 2·8400, $d_{4°}^{59·0°}$ 2·7935, $d_{4°}^{85·9°}$ 2·7251. Apparatus *D*.

24·8°	6·35	2·8755	45·10	227·8	60·1°	5·87	2·7909	40·46	228·4
41·7	6·04	2·8359	42·30	227·3				Mean	227·8

564. 1 : 2 : 3-*Tribromopropane.* B. p. 102°/18 mm.; *M* 280·83; n_C 1·58191, n_D 1·58633, n_F 1·59728, $n_{G'}$ 1·60551; R_C 38·69, R_D 38·93, R_F 39·52, $R_{G'}$ 39·96; $Mn_D^{20°}$ 445·48. Densities determined: $d_{4°}^{20°}$ 2·4222, $d_{4°}^{41·4°}$ 2·3861, $d_{4°}^{60·9°}$ 2·3457, $d_{4°}^{86·5°}$ 2·2919. Apparatus *A*.

17·5°	10·07	2·4271	45·77	301·7	62·0°	9·19	2·3437	40·33	302·0
41·5	9·54	2·3859	42·62	301·5	87·7	8·58	2·2897	36·79	302·8
								Mean	302·0

565. *Ethyl orthoformate.* B. p. 143°/765 mm.; *M* 148·20; n_C 1·38792, n_D 1·38979, n_F 1·39428, $n_{G'}$ 1·39738; R_C 39·13, R_D 39·30, R_F 39·71, $R_{G'}$ 39·98; $Mn_D^{20°}$ 205·97. Densities determined: $d_{4°}^{20°}$ 0·8934, $d_{4°}^{41·1°}$ 0·8722, $d_{4°}^{60·7°}$ 0·8530, $d_{4°}^{87·3°}$ 0·8245. Apparatus *D*.

17·1°	10·81	0·8963	23·93	365·7	60·7°	9·26	0·8530	19·50	365·2
21·9	10·68	0·8915	23·51	366·1	85·6	8·44	0·8262	17·22	365·4
40·7	9·91	0·8726	21·36	365·1				Mean	365·5

566. n-*Propyl orthoformate.* B. p. 91°/17 mm.; *M* 190·28; n_C 1·40512, n_D 1·40711, n_F 1·41188, $n_{G'}$ 1·41534; R_C 53·05, R_D 53·28, R_F 53·83, $R_{G'}$ 54·22; $Mn_D^{20°}$ 267·74. Densities determined: $d_4^{20°}$ 0·8794, $d_4^{41·4°}$ 0·8605, $d_4^{61·0°}$ 0·8427, $d_4^{87·9°}$ 0·8204. Apparatus *D*.

t.	*H.*	$d_4^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_4^{t°}$.	γ.	*P.*
13·4°	11·64	0·8853	25·45	482·7	41·4°	10·72	0·8605	22·78	483·1
17·4	11·50	0·8817	25·04	482·8	61·0	10·09	0·8427	21·00	483·4
20·0	11·41	0·8794	24·78	482·8	86·8	9·25	0·8196	18·72	482·9
								Mean	483·0

567. n-*Butyl orthoformate.* B. p. 127°/16 mm.; *M* 232·35; n_C 1·41603, n_D 1·41806, n_F 1·42302, $n_{G'}$ 1·42654; R_C 66·92, R_D 67·21, R_F 67·90, $R_{G'}$ 68·40; $Mn_D^{20°}$ 329·50. Densities determined: $d_4^{20°}$ 0·8713, $d_4^{41·4°}$ 0·8540, $d_4^{61·7°}$ 0·8382, $d_4^{85°1°}$ 0·8188. Apparatus *D*.

17·1°	12·02	0·8732	25·92	600·4	41·0°	11·25	0·8543	23·68	600·3
22·0	11·85	0·8697	25·45	600·1	60·9	10·60	0·8388	21·96	599·6
27·8	11·72	0·8651	25·04	600·8	86·8	9·88	0·8174	19·94	600·7
								Mean	600·3

568. *Thionyl chloride.* B. p. 76·5°/768 mm.; *M* 118·97; n_C 1·51593, n_D 1·52048, n_F 1·53310, $n_{G'}$ 1·5432 (somewhat doubtful); R_C 21·95, R_D 22·12, R_F 22·56, $R_{G'}$ 22·98; $Mn_D^{20°}$ 180·06. Densities determined: $d_4^{20°}$ 1·6366, $d_4^{41·6°}$ 1·5972, $d_4^{59·9°}$ 1·5645. Apparatus *E*.

18·3°	8·78	1·6397	33·53	174·6	40·8°	8·19	1·5987	30·49	175·0
20·8	8·68	1·6351	33·05	174·5	59·1	7·59	1·5641	27·65	174·7
								Mean	174·7

[Sugden, Reed, and Wilkins (*loc. cit.*) find $d_4^{20°}$ (extrap.) 1·645 and *P* 174·5.]

569. *Sulphuryl chloride.* B. p. 69·5°/775 mm.; *M* 134·97; n_C 1·44049, n_D 1·44325, n_F 1·45005, $n_{G'}$ 1·45508; R_C 21·31, R_D 21·43, R_F 21·71, $R_{G'}$ 21·92; $Mn_D^{20°}$ 194·80. Densities determined: $d_4^{20°}$ 1·6708, $d_4^{41·8°}$ 1·6217. Apparatus *A*.

16·1°	9·63	1·6796	30·29	188·5	26·6°	9·22	1·6560	28·59	188·6
17·9	9·59	1·6755	30·09	188·7	41·6	8·69	1·6221	26·39	187·7
								Mean	188·4

Sugden, Reed, and Wilkins (*loc. cit.*) give $d_4^{20°}$ (extrap.) 1·682, *P* 193·3 for a specimen prepared from chlorosulphonic acid. In view of the disparity in density and large difference in surface tension from the author's results, another specimen of pure sulphuryl chloride was prepared from an independent source of commercially pure material by careful fractionation through a Widmer column in an all-glass apparatus; the sample for the surface-tension measurements was collected directly in the surface-tension apparatus and the usual precautions against exposure to the atmosphere were taken throughout. The original results were adequately confirmed and it would appear that Sugden, Reed, and Wilkins's sample was impure. The results for the highly purified sample were as follows: b. p. 69°/763 mm.; n_C 1·44065, n_D 1·44340, n_F 1·45024, $n_{G'}$ 1·45533; R_C 21·31, R_D 21·43, R_F 21·71, $R_{G'}$ 21·93; $Mn_D^{20°}$ 194·82. Densities determined: $d_4^{20°}$ 1·6712, $d_4^{40·6°}$ 1·6264. Apparatus *F*.

18·7°	7·65	1·6740	29·82	188·4	40·5°	7·08	1·6266	26·81	189·0
25·3	7·36	1·6596	28·44	187·9				Mean	188·4

570. *Phosphorus trichloride.* B. p. 75°/772 mm.; M 137·35; n_C 1·51039, n_D 1·51473, n_F 1·52576, $n_{G'}$ 1·53467; R_C 26·08, R_D 26·27, R_F 26·74, $R_{G'}$ 27·11; $Mn_D^{20°}$ 208·04. Densities determined: $d_4^{20°}$ 1·5761, $d_4^{43·8°}$ 1·5332, $d_4^{61·8°}$ 1·5008. Apparatus *E*.

15·3°	7·92	1·5847	29·23	201·5	41·6°	7·23	1·5367	25·88	201·8
19·2	7·83	1·5776	28·77	201·7	60·3	6·72	1·5030	23·52	201·7
25·5	7·62	1·5660	27·79	201·5				Mean	201·6

571. *Phosphorus oxychloride.* B. p. 106·5°/775 mm.; *M* 153·35; n_C 1·45917, n_D 1·46085, n_F 1·46746, $n_{G'}$ 1·47240; R_C 24·97, R_D 25·05, R_F 25·36, $R_{G'}$ 25·59; $Mn_D^{20°}$ 224·03. Densities determined: $d_4^{20°}$ 1·6795, $d_4^{40·7°}$ 1·6414, $d_4^{60·8°}$ 1·6045, $d_4^{85·1°}$ 1·5580. Apparatus *A*.

14·9°	10·54	1·6890	33·33	218·2	61·9°	9·09	1·6025	27·28	218·9
20·5	10·40	1·6786	32·69	218·4	86·4	8·33	1·5556	24·26	219·2
41·2	9·72	1·6405	29·86	218·5				Mean	218·6

[Sugden, Reed, and Wilkins (*loc. cit.*) give $d_4^{20°}$ (extrap.) 1·680, *P* 217·6.]

572. *Phosphorus tribromide.* B. p. 171·5°/763 mm.; *M* 270·73; n_D 1·69632; R_D 36·07; $Mn_D^{20°}$ 459·24. Densities determined: $d_4^{20°}$ 2·8903, $d_4^{41·0°}$ 2·8420, $d_4^{60·0°}$ 2·7965, $d_4^{83·0°}$ 2·7364. Apparatus *A*.

15·6°	7·97	2·9006	43·29	239·4	59·5°	7·18	2·7977	37·61	239·7
41·4	7·55	2·8411	40·17	239·8				Mean	239·7

[Sugden, Reed, and Wilkins (*loc. cit.*) give $d_4^{20°}$ (extrap.) 2·893, *P* 242·9.]

573. *Dimethylnitrosoamine.* B. p. 151°/767 mm.; M 74·09; n_C 1·43210, n_D 1·43580, n_F 1·44544, $n_{G'}$ 1·45360 (line faint); R_C 19·12, R_D 19·27, R_F 19·64, $R_{G'}$ 19·95; $Mn_D^{20°}$ 106·38. Densities determined: $d_{4°}^{20°}$ 1·0050, $d_{4°}^{42·6°}$ 0·9837, $d_{4°}^{60·0°}$ 0·9668, $d_{4°}^{85·6°}$ 0·9408. Apparatus *D*.

t.	*H.*	$d_{4°}^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	γ.	*P.*
16·3°	15·55	1·0086	38·73	183·3	60·8°	13·96	0·9660	33·29	184·2
21·9	15·44	1·0031	38·25	183·7	86·8	12·97	0·9396	30·10	184·7
40·8	14·69	0·9854	35·75	183·8				Mean	183·9

574. *Diethylnitrosoamine.* B. p. 174·5°/777 mm.; M 102·14; n_C 1·43468, n_D 1·43791, n_F 1·44640, $n_{G'}$ 1·45347; R_C 28·25, R_D 28·43, R_F 28·91, $R_{G'}$ 29·31; $Mn_D^{20°}$ 146·87. Densities determined: $d_{4°}^{20°}$ 0·9428, $d_{4°}^{40·3°}$ 0·9255, $d_{4°}^{60·0°}$ 0·9082, $d_{4°}^{86·7°}$ 0·8842. Apparatus *D*.

16·4°	14·30	0·9459	33·40	259·6	63·0°	12·81	0·9108	28·81	259·8
21·2	14·16	0·9417	32·93	259·8	87·8	11·95	0·8832	26·06	261·3
41·8	13·52	0·9242	30·86	260·5				Mean	259·8

575. *Di*-n-*propylnitrosoamine.* B. p. 89°/13 mm.; M 130·19; n_C 1·44059, n_D 1·44365, n_F 1·45155, $n_{G'}$ 1·45804; R_C 37·50, R_D 37·73, R_F 38·31, $R_{G'}$ 38·78; $Mn_D^{20°}$ 187·96. Densities determined: $d_{4°}^{20°}$ 0·9160, $d_{4°}^{41·6°}$ 0·8992, $d_{4°}^{61·1°}$ 0·8830, $d_{4°}^{86·9°}$ 0·8624. Apparatus *A*.

19·1°	18·46	0·9167	31·69	337·0	61·2°	16·69	0·8829	27·59	338·0
25·0	18·25	0·9120	31·17	337·3	86·5	15·76	0·8627	25·46	339·0
41·9	17·58	0·8990	29·59	337·8				Mean	337·8

576. *Di*-n-*butylnitrosoamine.* B. p. 125—125·5°/21 mm.; M 158·24; n_C 1·44454, n_D 1·44746, n_F 1·45497, $n_{G'}$ 1·46109; R_C 46·70, R_D 46·98, R_F 47·66, $R_{G'}$ 48·21; $Mn_D^{20°}$ 229·05. Densities determined: $d_{4°}^{20°}$ 0·9009, $d_{4°}^{41·9°}$ 0·8838, $d_{4°}^{61·7°}$ 0·8686, $d_{4°}^{86·5°}$ 0·9498. Apparatus *D*.

17·3°	13·72	0·9030	30·60	412·1	62·3°	12·45	0·8682	26·69	414·3
21·0	13·61	0·9001	30·25	412·3	88·0	11·67	0·8487	24·46	414·6
42·0	13·06	0·8837	28·46	413·6				Mean	413·4

577. *Nitromethane.* B. p. 101°/762 mm.; M 61·04; n_C 1·37895, n_D 1·38152, n_F 1·38778, $n_{G'}$ 1·39270; R_C 12·29, R_D 12·36, R_F 12·54, $R_{G'}$ 12·69; $Mn_D^{20°}$ 83·55. Densities determined: $d_{4°}^{20°}$ 1·1371, $d_{4°}^{41·1°}$ 1·1081, $d_{4°}^{60·9°}$ 1·0815. Apparatus *A*.

17·3°	17·43	1·1408	37·23	132·2	41·2°	16·24	1·1080	33·69	133·0
20·7	17·26	1·1361	36·72	132·3	60·9	15·25	1·0815	30·88	133·1
25·9	17·06	1·1290	36·07	132·5				Mean	132·6

578. *Nitroethane.* B. p. 114°/765 mm.; M 75·08; n_C 1·38936, n_D 1·39173, n_F 1·39765, $n_{G'}$ 1·40212; R_C 16·93, R_D 17·02, R_F 17·25, $R_{G'}$ 17·42; $Mn_D^{20°}$ 104·49. Densities determined: $d_{4°}^{20°}$ 1·0497, $d_{4°}^{41°}$ 1·0250, $d_{4°}^{59·8°}$ 1·0026, $d_{4°}^{85·0°}$ 0·9726. Apparatus *D*.

20·2°	12·42	1·0477	32·14	170·7	61·4°	10·98	1·0007	27·14	171·2
25·0	12·29	1·0437	31·68	170·7	87·3	10·03	0·9699	24·02	171·6
41·3	11·66	1·0247	29·50	170·8				Mean	171·0

579. 1-*Nitro*-n-*propane.* B. p. 130·5°/761 mm.; M 89·10; n_C 1·39816, n_D 1·40130, n_F 1·40639, $n_{G'}$ 1·41083; R_C 21·50, R_D 21·64, R_F 21·89, $R_{G'}$ 22·15; $Mn_D^{20°}$ 124·86. Densities determined: $d_{4°}^{20°}$ 1·0009, $d_{4°}^{41·1°}$ 0·9794, $d_{4°}^{61·8°}$ 0·9573, $d_{4°}^{87·0°}$ 0·9296. Apparatus *A*.

17·1°	16·31	1·0039	30·66	208·8	61·7°	14·34	0·9571	25·70	209·6
20·1	16·13	1·0008	30·23	208·8	86·7	13·25	0·9299	23·07	210·0
41·3	15·32	0·9792	28·09	209·5				Mean	209·3

580. 2-*Nitro*-n-*propane.* B. p. 119·5°/752 mm.; M 89·10; n_C 1·39196, n_D 1·39426, n_F 1·39992, $n_{G'}$ 1·40418; R_C 21·48, R_D 21·59, R_F 21·87, $R_{G'}$ 22·08; $Mn_D^{20°}$ 124·23. Densities determined: $d_{4°}^{20°}$ 0·9876, $d_{4°}^{41·6°}$ 0·9652, $d_{4°}^{60·3°}$ 0·9453, $d_{4°}^{86·8°}$ 0·9162. Apparatus *A*.

21·0°	15·74	0·9865	29·08	209·7	61·1°	13·87	0·9445	24·53	209·9
29·1	15·40	0·9781	28·20	209·9	86·0	12·73	0·9170	21·86	210·1
41·2	14·80	0·9656	26·76	209·7				Mean	209·8

581. 1-*Nitro*-n-*butane.* B. p. 151·5—152·5°/780 mm.; M 103·12; n_C 1·40975, n_D 1·41028, n_F 1·41613, $n_{G'}$ 1·42048; R_C 26·20, R_D 26·33, R_F 26·65, $R_{G'}$ 26·90; $Mn_D^{20°}$ 145·43. Densities determined: $d_{4°}^{20°}$ 0·9710, $d_{4°}^{41·2°}$ 0·9514, $d_{4°}^{60·0°}$ 0·9335, $d_{4°}^{87·0°}$ 0·9067. Apparatus *A*.

15·4°	16·34	0·9753	29·84	247·1	41·6°	15·29	0·9510	27·23	247·7
20·3	16·15	0·9707	29·35	247·3	62·1	14·52	0·9312	25·32	248·4
25·9	16·05	0·9654	29·01	247·9	87·5	13·43	0·9062	22·79	248·6
								Mean	247·8

582. 1-*Nitro*-n-*pentane*. B. p. 66°/16 mm.; M 117·15; n_C 1·41516, n_D 1·41751, n_F 1·42329, $n_{G'}$ 1·42771; R_C 30·81, R_D 30·96, R_F 31·34, $R_{G'}$ 31·62; $Mn_D^{20°}$ 166·06. Densities determined: $d_4^{20°}$ 0·9525, $d_4^{41·6°}$ 0·9330, $d_4^{63·6°}$ 0·9137, $d_4^{86·6°}$ 0·8912. Apparatus *D*.

t.	*H.*	d_4^t.	γ.	*P.*	*t.*	*H.*	d_4^t.	γ.	*P.*
17·0°	12·53	0·9552	29·55	286·0	62·3°	11·19	0·9143	25·27	287·3
25·3	12·36	0·9477	28·93	286·7	88·3	10·40	0·8901	22·86	287·8
41·5	11·81	0·9331	27·21	286·8				Mean	286·9

583. 1-*Nitro*-n-*hexane*. B. p. 81·5°/15 mm.; M 131·18; n_C 1·42111, n_D 1·42346, n_F 1·42930, $n_{G'}$ 1·43366; R_C 35·41, R_D 35·59, R_F 36·01, $R_{G'}$ 36·34; $Mn_D^{20°}$ 186·73. Densities determined: $d_4^{20°}$ 0·9396, $d_4^{41·3°}$ 0·9219, $d_4^{62·6°}$ 0·9043, $d_4^{85·5°}$ 0·8845. Apparatus *D*.

20·5°	12·77	0·9392	29·62	325·8	62·5°	11·53	0·9044	25·75	326·7
42·2	12·07	0·9212	27·46	326·0	86·7	10·90	0·8835	23·78	327·9
								Mean	326·6

584. *Nitrobenzene*. B. p. 207·5°/760 mm.; M 123·13; n_C 1·54559, n_D 1·55246, n_F 1·57086, $n_{G'}$ 1·58972 (line faint); R_D 32·38, R_D 32·72, R_F 33·62, $R_{G'}$ 34·44; $Mn_D^{20°}$ 191·13. Densities determined: $d_4^{20°}$ 1·2031, $d_4^{1·8°}$ 1·1829, $d_4^{61·7°}$ 1·1641, $d_4^{86·6°}$ 1·1402. Apparatus *A*.

16·3°	19·72	1·2066	44·55	263·6	60·5°	17·94	1·1652	39·14	264·3
19·5	19·56	1·2036	44·08	263·6	86·5	16·86	1·1403	36·00	264·4
40·9	18·69	1·1834	41·42	263·9				Mean	263·9

585. n-*Butyl nitrite*. B. p. 27°/88 mm.; M 103·12; n_C 1·37463, n_D 1·37683, n_F 1·38241, $n_{G'}$ 1·38678; R_C 26·73, R_D 26·87, R_F 27·22; $R_{G'}$ 27·50; $Mn_D^{20°}$ 141·98. Densities determined: $d_4^{20°}$ 0·8823, $d_4^{40·9°}$ 0·8575. Apparatus *A*.

13·5°	13·07	0·8900	21·78	250·3	23·6°	12·76	0·8780	20·98	251·4
17·7	12·96	0·8850	21·48	250·8	41·3	11·76	0·8570	18·87	251·1
								Mean	250·9

586. n-*Amyl nitrite*. B. p. 104·5°/763 mm. and 29°/40 mm.; M 117·15; n_C 1·38707, n_D 1·38931, n_F 1·39498, $n_{G'}$ 1·39935; R_C 31·28, R_D 31·44, R_F 31·84, $R_{G'}$ 32·16; $Mn_D^{20°}$ 162·76. Densities determined: $d_4^{20°}$ 0·8820, $d_4^{40·7°}$ 0·8603, $d_4^{63·7°}$ 0·8352. Apparatus *A*.

13·4°	14·06	0·8890	23·41	289·8	41·5°	12·72	0·8595	20·47	289·9
16·5	13·90	0·8857	23·05	289·8	58·2	11·83	0·8410	18·63	289·4
22·1	13·76	0·8798	22·67	290·5				Mean	289·9

587. n-*Hexyl nitrite*. B. p. 129·5—130°/761 mm. and 52°/44 mm.; M 131·17; n_C 1·39619, n_D 1·39846, n_F 1·40412, $n_{G'}$ 1·40853; R_C 35·92, R_D 36·10, R_F 36·55, $R_{G'}$ 36·90; $Mn_D^{20°}$ 183·44. Densities determined: $d_4^{20°}$ 0·8778, $d_4^{41·4°}$ 0·8572, $d_4^{61·7°}$ 0·8371. Apparatus *D*.

16·3°	11·10	0·8814	24·16	329·9	42·1°	10·22	0·8565	21·62	331·0
19·2	11·02	0·8786	23·91	330·1	62·0	9·50	0·8368	19·63	330·0
24·7	10·90	0·8732	23·51	330·8				Mean	330·4

588. *Ethyl nitrate*. B. p. 88°/757 mm.; M 91·07; n_C 1·38294, n_D 1·38528, n_F 1·39091, $n_{G'}$ 1·39526; R_C 19·18, R_D 19·28, R_F 19·53, $R_{G'}$ 19·73; $Mn_D^{20°}$ 126·16. Densities determined: $d_4^{20°}$ 1·1076, $d_4^{40·6°}$ 1·0809. Apparatus *F*.

18·3°	10·97	1·1098	28·34	189·3	41·5°	10·03	1·0797	25·21	189·1
31·3	10·47	1·0929	26·64	189·3				Mean	189·2

589. n-*Propyl nitrate*. B. p. 110°/762 mm.; M 105·10; n_C 1·39491, n_D 1·39725, n_F 1·40287, $n_{G'}$ 1·40706; R_C 23·91, R_D 24·03, R_F 24·33, $R_{G'}$ 24·56; $Mn_D^{20°}$ 146·86. Densities determined: $d_4^{20°}$ 1·0538, $d_4^{40·6°}$ 1·0316, $d_4^{59·7°}$ 1·0066. Apparatus *F*.

17·8°	11·16	1·0563	27·45	227·7	40·9°	10·19	1·0316	24·45	226·8
22·3	11·04	1·0512	27·02	227·9	58·4	9·60	1·0081	22·53	227·1
								Mean	227·5

590. n-*Butyl nitrate*. B. p. 135—135·5°/763 mm.; M 119·12; n_C 1·40413, n_D 1·40647, n_F 1·41211, $n_{G'}$ 1·41653; R_C 28·49, R_D 28·64, R_F 28·99, $R_{G'}$ 29·26; $Mn_D^{20°}$ 167·54. Densities determined; $d_4^{20°}$ 1·0228, $d_4^{40·6°}$ 1·0018, $d_4^{60·7°}$ 0·9791. Apparatus *F*.

13·9°	11·98	1·0293	28·71	267·9	41·8°	10·97	0·9999	25·54	267·8
18·5	11·80	1·0244	28·40	268·4	60·4	10·35	0·9794	23·60	268·1
								Mean	268·1

591. *Dimethyl carbonate*. B. p. 89·5°/755 mm.; M 90·07; n_C 1·36700, n_D 1·36874, n_F 1·37288, $n_{G'}$ 1·37568; R_C 18·89, R_D 18·97, R_F 19·16, $R_{G'}$ 19·29; $Mn_D^{20°}$ 123·28. Densities determined: $d_4^{20°}$ 1·0706, $d_4^{40·4°}$ 1·0446, $d_4^{58·8°}$ 1·0205. Apparatus *A*.

19·3°	14·63	1·0715	29·35	195·7	61·3°	12·45	1·0170	23·71	195·7
42·1	13·47	1·0424	26·29	195·7				Mean	195·5

592. *Diethyl carbonate.* B. p. 125·5°/758 mm.; *M* 118·13; n_C 1·38248, n_D 1·38433, n_F 1·38872, $n_{G'}$ 1·39183; R_C 28·19, R_D 28·31, R_F 28·59, $R_{G'}$ 28·80; $Mn_D^{20°}$ 163·53. Densities determined: $d_4^{20°}$ 0·9764, $d_4^{41·5°}$ 0·9521, $d_4^{61·7°}$ 0·9302, $d_4^{85·7°}$ 0·9024. Apparatus *D*.

t.	*H.*	$d_4^{t°}$.	γ.	*P.*	*t.*	*H.*	$d_4^{t°}$.	γ.	*P.*
13·2°	11·22	0·9840	27·27	274·3	41·6°	10·21	0·9520	24·00	274·7
16·4	11·03	0·9804	26·71	273·9	61·2	9·50	0·9309	21·79	274·2
23·1	10·88	0·9729	26·14	274·5	87·2	8·59	0·9007	19·11	274·2
								Mean	274·3

593. *Di*-n-*propyl carbonate.* B. p. 165°/752 mm.; *M* 146·18; n_C 1·39876, n_D 1·40072, n_F 1·40543, $n_{G'}$ 1·40885; R_C 37·48, R_D 37·64, R_F 38·03, $R_{G'}$ 38·32; $Mn_D^{20°}$ 204·75. Densities determined: $d_4^{20°}$ 0·9429, $d_4^{41·0°}$ 0·9232, $d_4^{61·2°}$ 0·9032, $d_4^{87·1°}$ 0·8769. Apparatus *D*.

19·3°	11·60	0·9436	27·03	353·2	60·8°	10·18	0·9036	22·72	353·2
21·9	11·52	0·9441	26·77	353·3	87·3	9·30	0·8767	20·14	353·2
41·2	10·81	0·9230	24·64	352·9					
								Mean	353·2

594. *Di*-n-*butyl carbonate.* B. p. 204·5°/758 mm.; *M* 174·23; n_C 1·40966, n_D 1·41167, n_F 1·41656, $n_{G'}$ 1·42000; R_C 46·64, R_D 46·84, R_F 47·33, $R_{G'}$ 47·66; $Mn_D^{20°}$ 245·96. Densities determined: $d_4^{20°}$ 0·9251, $d_4^{40·8°}$ 0·9057, $d_4^{61·0°}$ 0·8883, $d_4^{87·0°}$ 0·8638. Apparatus *A*.

16·8°	15·83	0·9280	27·51	430·0	61·5°	13·99	0·8878	23·26	431·0
23·0	15·61	0·9223	26·96	430·5	87·0	12·94	0·8638	20·93	431·4
41·4	14·81	0·9052	25·10	430·8					
								Mean	430·7

595. *Diisobutyl carbonate.* B. p. 187·5°/763 mm.; *M* 174·23; n_C 1·40529, n_D 1·40731, n_F 1·41212, $n_{G'}$ 1·41567; R_C 46·77, R_D 46·97, R_F 47·46, $R_{G'}$ 47·82; $Mn_D^{20°}$ 245·19. Densities determined: $d_4^{20°}$ 0·9137, $d_4^{40·5°}$ 0·8945, $d_4^{62·1°}$ 0·8744, $d_4^{85·0°}$ 0·8517. Apparatus *A*.

14·5°	15·00	0·9189	25·81	427·4	61·3°	13·12	0·8752	21·50	428·7
41·0	13·96	0·8940	23·37	428·5	86·3	12·02	0·8505	19·14	428·5
								Mean	428·3

596. *Methyl thiocyanate.* B. p. 130·5°/765 mm.; *M* 73·11; n_C 1·46523, n_D 1·46854, n_F 1·47658, $n_{G'}$ 1·48278; R_C 18·82, R_D 18·93, R_F 19·21, $R_{G'}$ 19·43; $Mn_D^{20°}$ 107·36. Densities determined: $d_4^{20°}$ 1·0744, $d_4^{40·9°}$ 1·0504, $d_4^{61·3°}$ 1·0281, $d_4^{86·5°}$ 0·9985. Apparatus *D*.

15·3°	14·39	1·0798	38·37	168·5	42·5°	13·43	1·0486	34·78	168·5
21·3	14·19	1·0729	37·60	168·7	60·9	12·77	1·0285	32·44	169·6
23·7	14·09	1·0702	27·24	168·8	85·2	11·83	1·0000	29·22	170·1
								Mean	169·0

597. *Ethyl thiocyanate.* B. p. 145·5°/765 mm.; *M* 87·14; n_C 1·45998, n_D 1·46304, n_F 1·47070, $n_{G'}$ 1·47656; R_C 23·59, R_D 23·72, R_F 24·06, $R_{G'}$ 24·30; $Mn_D^{20°}$ 127·49. Densities determined: $d_4^{20°}$ 1·0116, $d_4^{41·1°}$ 0·9896, $d_4^{60·6°}$ 0·9704, $d_4^{87·0°}$ 0·9426. Apparatus *A*.

14·4°	17·84	1·0174	33·99	206·8	41·1°	16·63	0·9896	30·82	207·4
19·9	17·53	1·0117	33·21	206·8	61·2	15·80	0·9698	28·69	208·0
27·2	17·30	1·0042	32·53	207·2	87·0	14·64	0·9426	25·84	208·4
								Mean	207·4

598. n-*Propyl thiocyanate.* B. p. 164·5°/760 mm.; *M* 101·17; n_C 1·46016, n_D 1·46314, n_F 1·47050, $n_{G'}$ 1·47621; R_C 28·24, R_D 28·39, R_F 28·78, $R_{G'}$ 29·08; $Mn_D^{20°}$ 148·02. Densities determined: $d_4^{20°}$ 0·9817, $d_4^{40·6°}$ 0·9627, $d_4^{60·8°}$ 0·9439, $d_4^{81·9°}$ 0·9233. Apparatus *D*.

17·9°	13·52	0·9837	32·84	246·2	60·9°	12·19	0·9433	28·40	247·6
25·4	13·41	0·9767	32·35	247·0	86·8	11·38	0·9187	25·82	248·2
41·5	12·83	0·9619	30·48	247·1					
								Mean	247·2

599. n-*Butyl thiocyanate.* B. p. 184°/770 mm.; *M* 115·19; n_C 1·46099, n_D 1·46389, n_F 1·47108, $n_{G'}$ 1·47660; R_C 32·89, R_D 33·07, R_F 33·51, $R_{G'}$ 33·84; $Mn_D^{20°}$ 168·63. Densities determined: $d_4^{20°}$ 0·9610, $d_4^{40·5°}$ 0·9433, $d_4^{60·8°}$ 0·9252, $d_4^{85·2°}$ 0·9035. Apparatus *A*.

19·2°	17·81	0·9617	32·07	285·0	60·5°	16·21	0·9255	28·09	286·5
26·5	17·56	0·9553	31·41	285·5	85·1	15·25	0·9036	25·80	287·4
40·4	16·96	0·9434	29·96	285·7					
								Mean	286·0

600. *Ethyl* iso*thiocyanate.* B. p. 132—132·5°/762 mm.; *M* 87·14; n_C 1·49877, n_D 1·50435, n_F 1·51495, $n_{G'}$ 1·52432; R_C 25·69, R_D 25·92, R_F 26·38, $R_{G'}$ 26·78; $Mn_D^{20°}$ 131·09. Densities determined: d_4^{20} 0·9962, $d_4^{42·0°}$ 0·9740, $d_4^{60·8°}$ 0·9545, $d_4^{87·1°}$ 0·9269. Apparatus *D*.

16·4°	13·49	0·9999	33·31	209·4	60·2°	12·00	0·9551	28·30	210·4
19·2	13·42	0·9970	33·04	209·6	86·3	11·08	0·9277	25·38	210·8
41·3	12·67	0·9747	30·50	210·1					
								Mean	210·1

601. *Allyl* isothiocyanate. B. p. 151—151·5°/768 mm.; *M* 99·19, n_C 1·52179, n_D 1·52686, n_F 1·53970, $n_{G'}$ 1·54982, R_C 29·89, R_D 30·13, R_F 30·74, $R_{G'}$ 31·22; $Mn_D^{20°}$ 151·45. Densities determined: $d_{4°}^{20°}$ 1·0118, $d_{4°}^{40·0°}$ 0·9927, $d_{4°}^{60·9°}$ 0·9723, $d_{4°}^{85·5°}$ 0·9472. Apparatus *A*.

t.	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*	*t.*	*H.*	$d_{4°}^{t°}$.	*γ.*	*P.*
21·0°	17·95	1·0108	33·97	236·9	60·9°	16·12	0·9723	29·35	237·4
28·1	17·73	1·0039	33·36	237·2	85·6	15·11	0·9471	26·80	238·3
40·7	17·02	0·9920	31·61	237·1				Mean	237·4

602. *Diethyl xanthate.* B. p. 70·2°/4·9 mm.; *M* 150·25; n_C 1·52775, n_D 1·53325, n_F 1·54795, $n_{G'}$ 1·56079; R_C 42·68, R_D 43·05, R_F 44·04, $R_{G'}$ 44·88; $Mn_D^{20°}$ 230·38. Densities determined: $d_{4°}^{20°}$ 1·0837, $d_{4°}^{41·0°}$ 1·0647, $d_{4°}^{61·7°}$ 1·0451, $d_{4°}^{86·9°}$ 1·0213. Apparatus *D*.

19·2°	12·82	1·0844	34·33	335·4	60·2°	11·55	1·0446	29·80	336·1
25·4	12·68	1·0787	33·78	335·8	86·7	10·83	1·0215	27·32	336·3
41·9	12·14	1·0639	31·90	335·6				Mean	335·8

603. *Di*-n-*propyl xanthate.* B. p. 91·1°/4·5 mm.; *M* 178·30; n_C 1·51894, n_D 1·52396, n_F 1·53741, $n_{G'}$ 1·54895; R_C 52·29, R_D 52·72, R_F 53·84, $R_{G'}$ 54·80; $Mn_D^{20°}$ 271·73. Densities determined: $d_{4°}^{20°}$ 1·0349, $d_{4°}^{41·3°}$ 1·0165, $d_{4°}^{61·9°}$ 0·9992, $d_{4°}^{87·1°}$ 0·9767. Apparatus *A*.

20·9°	16·92	1·0341	32·76	412·5	61·5°	15·40	0·9995	28·82	413·3
28·0	16·68	1·0280	32·11	412·9	87·4	14·39	0·9764	26·31	413·6
40·8	16·18	1·0169	30·81	413·1				Mean	413·1

604. *Ethyl* S-n-*butylxanthate.* B. p. 90·3°/4·0 mm.; *M* 178·30; n_C 1·51865, n_D 1·52368, n_F 1·53710, $n_{G'}$ 1·54872; R_C 52·27, R_D 52·69, R_F 53·82, $R_{G'}$ 54·78; $Mn_D^{20°}$ 271·68. Densities determined: $d_{4°}^{20}$ 1·0349, $d_{4°}^{42·2°}$ 1·0162, $d_{4°}^{61·4°}$ 1·0002, $d_{4°}^{87·0°}$ 0·9774. Apparatus *D*.

18·0°	12·91	1·0366	33·05	412·4	60·6°	11·71	1·0007	28·94	413·3
23·6	12·73	1·0318	32·44	412·4	86·1	11·04	0·9783	26·67	414·2
42·3	12·20	1·0161	30·61	412·8				Mean	413·0

605. n-*Butyl* S-*ethylxanthate.* B. p. 91·0°/4·3 mm.; *M* 178·30; n_C 1·51869, n_D 1·52372, n_F 1·53718, $n_{G'}$ not visible; R_C 52·26, R_D 52·68, R_F 53·81; $Mn_D^{20°}$ 217·68. Densities determined: $d_{4°}^{20°}$ 1·0351, $d_{4°}^{42·0°}$ 1·0164, $d_{4°}^{61·7°}$ 1·0001, $d_{4°}^{87·0°}$ 0·9777. Apparatus *A*.

18·3°	16·97	1·0365	32·94	412·1	61·1°	15·38	1·0006	28·82	412·9
29·8	16·79	1·0268	32·28	413·9	84·8	14·56	0·9796	26·71	413·8
40·9	16·12	1·0173	30·71	412·6				Mean	413·1

606. *Di*-n-*butyl xanthate.* B. p. 117°/4·0 mm.; *M* 206·35; n_C 1·50994, n_D 1·51456, n_F 1·52681, $n_{G'}$ 1·53704; R_C 61·59, R_D 62·07, R_F 63·30, $R_{G'}$ 64·32; $Mn_D^{20°}$ 312·55. Densities determined: $d_{4°}^{20°}$ 1·0019, $d_{4°}^{41·0°}$ 0·9855, $d_{4°}^{60·8°}$ 0·9691, $d_{4°}^{87·4°}$ 0·9475. Apparatus *A*.

15·9°	17·13	1·0052	32·24	489·2	41·3°	16·23	0·9852	29·94	490·0
20·3	17·03	1·0017	31·94	489·8	60·9	15·43	0·9690	28·00	489·9
24·9	16·83	0·9980	31·45	489·7	86·9	14·61	0·9479	25·93	491·3
								Mean	489·8

The author's thanks are due to Imperial Chemical Industries for the liberal grants in support of the investigations described in Parts XVIII—XXIII, and to Dr. G. H. Jeffery, F.R.I.C., for the preparation and purification of the alkyl nitrates.

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370. *Pyrazine Derivatives. Part V. A General Method for the Synthesis of Aminopyrazine Derivatives.*

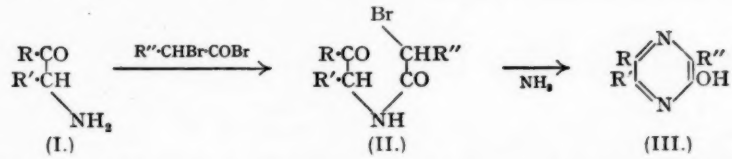
By G. T. NEWBOLD, F. S. SPRING, and W. SWEENY.

It is known that treatment of α-bromopropionyl derivatives of amino-ketones of the type $R{\cdot}CO{\cdot}CHR^1{\cdot}NH_2$ with ammonia gives rise to trisubstituted hydroxypyrazines (III). In contrast to this behaviour, it is now shown that α-bromopropionyl derivatives of amino-methyl ketones (*i.e.*, $R{\cdot}CO{\cdot}CH_2{\cdot}NH_2$) when treated with ammonia undergo a remarkable reaction to give 2-propionamidopyrazine derivatives [*e.g.*, (IV)] in high yield.

TOTA and ELDERFIELD (*J. Org. Chem.*, 1942, **7**, 317) have described a method for the synthesis of 5 : 6-disubstituted and 3 : 5 : 6-trisubstituted 2-hydroxypyrazines (III) in which a 2-(α-bromoacylamido)ketone (II) is treated with ammonia. The preparation of the α-bromoacyl derivative (II) of the unstable 2-amino-ketone (I) was effected by adding an aqueous solution of the hydrochloride of the amino-ketone to a suspension of calcium carbonate in chloroform and immediately

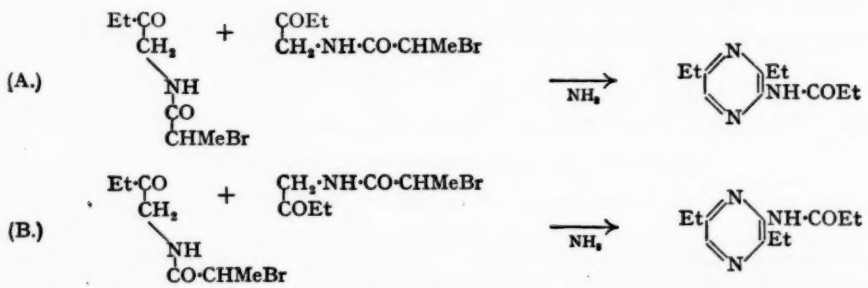
treating this mixture with a chloroform solution of the α-bromoacyl bromide. Using this method, Tota and Elderfield have prepared 2-hydroxy-5 : 6-dimethylpyrazine (III; R = R′ = Me, R″ = H), 2-hydroxy-5-phenyl-6-methylpyrazine (III; R = Ph, R′ = Me, R″ = H), 2-hydroxy-5-phenyl-6-methyl-3-ethylpyrazine (III; R = Ph, R′ = Me, R″ = Et), and 2-hydroxy-5-methyl-6-(2-hydroxyethyl)pyrazine (III; R = Me, R′ = HO·[CH_2]$_2$, R″ = H), and Newbold and Spring (*J.*, 1947, 373) have used it to prepare 2-hydroxy-3 : 5 : 6-trimethylpyrazine (III; R = R′ = R″ = Me).

In a general study of methods for the synthesis of hydroxypyrazines in connection with an examination of the antibacterial substance aspergillic acid, we have attempted to use the Tota and Elderfield method to prepare 2-hydroxy-3 : 5-dialkyl-substituted pyrazines. In the preparation of 2-(α-bromoacylamido)ketones, we find that considerable improvement in yield results (in the cases examined by us) if *N*-methylmorpholine is used instead of calcium carbonate, and the reaction is carried out under anhydrous conditions. Using this modified procedure, condensation of α-bromopropionyl bromide with the hydrochloride of 1-aminobutan-2-one (I; R = Et, R′ = H) gave the expected 1-(*α-bromopropionamido)butan-2-one* (II; R = Et,



(I.) (II.) (III.)

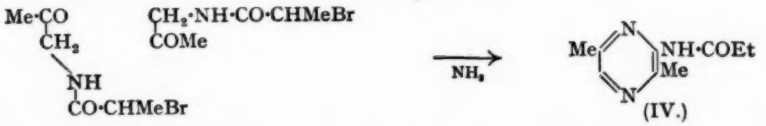
R″ = Me, R′ = H) in high yield. When treated with ammonia, this bromoacylamido-ketone gave a crystalline compound, $C_{11}H_{17}ON_3$, m. p. 98°, and not the expected 2-hydroxy-3-methyl-5-ethylpyrazine. The compound $C_{11}H_{17}ON_3$ does not show the characteristic properties of a hydroxypyrazine; it does not possess acidic properties, and its absorption spectrum exhibits maxima at 2260 A. and 2790 A., whereas alkyl-substituted hydroxypyrazines exhibit maxima at approximately 2280 A. and 3250 A. (Newbold and Spring *loc. cit.*). When heated with sodium hydroxide solution, the compound $C_{11}H_{17}ON_3$ gives a hygroscopic base, m. p. 42°, characterised as its *picrate*. Analysis of the picrate established the molecular formula $C_8H_{13}N_3$ for the parent base. A comparison of the absorption spectrum of this base with that of 2-amino-3 : 6-dimethylpyrazine (Baxter, Newbold, and Spring, this vol., p. 370) suggested that the former is an aminopyrazine and this was confirmed by treatment of the base with nitrous acid, whereby a hydroxypyrazine, m. p. 135°, was obtained, characterised by its ultra-violet absorption spectrum which exhibits maxima at 2270 A. and 3220 A. The relationship of the base and the compound $C_{11}H_{17}ON_3$ was established by treatment of the former with propionic anhydride, whereupon a propionyl derivative was obtained which proved to be identical with the compound $C_{11}H_{17}ON_3$. The compound $C_{11}H_{17}ON_3$ would thus appear to be a 2-propionamidodiethylpyrazine, and the base, $C_8H_{13}N_3$, a 2-aminodiethylpyrazine, and the reaction between ammonia and 1-(α-bromopropionamido)butan-2-one can be represented by one of the two expressions, (A) and (B).



If one of the expressions (A) and (B) is a true representation of the reaction, the formation of a propionamidopyrazine from an α-bromopropionamido-ketone and ammonia can only proceed if the parent amino-ketone is an aminomethyl ketone, *i.e.*, if the parent amino-ketone contains the grouping NH_2·CH_2·COR. The cases previously examined by Tota and Elderfield and by us before this investigation all employed substituted aminomethyl ketones of the type NH_2·CHR′·COR, and the products were all hydroxy-pyrazines. In such cases, reactions (A) and (B) are excluded since the necessary aromatisation involved in these reactions cannot occur.

In order to obtain general confirmation of these deductions, the reaction between ammonia and α-bromopropionyl derivatives of some other aminomethyl ketones has been examined.

Condensation of aminoacetone (I; R = Me, R′ = H) with α-bromopropionyl bromide in the presence of *N*-methylmorpholine gave *α-bromopropionamidoacetone* (II; R = R″ = Me, R′ = H) which, on treatment with ammonia, yielded a compound $C_9H_{12}ON_2$, m. p. 106—108°, and not a hydroxypyrazine. Hydrolysis of the compound, m. p. 106—108°, gave 2-amino-3 : 6-dimethylpyrazine, characterised by its picrate and by conversion into 2-hydroxy-3 : 6-dimethylpyrazine. Treatment of 2-amino-3 : 6-dimethylpyrazine with propionic anhydride gave *2-propionamido-3 : 6-dimethylpyrazine* (IV), which was identical with the compound, m. p. 106—108°. The reaction in this case is represented by the expression



(IV.)

By analogy, expression (B) is preferred for the reaction between ammonia and 1-(α-bromopropionamido)butan-2-one leading to the formulation of the compound $C_{11}H_{17}ON_3$ as *2-propionamido-3 : 6-diethylpyrazine*, the base $C_8H_{13}N_3$ as *2-amino-3 : 6-diethylpyrazine*, and the corresponding hydroxypyrazine, m. p. 135°, as *2-hydroxy-3 : 6-diethylpyrazine*. Confirmation of the structure of the compound has been obtained by its synthesis using a different route (Sharp and Spring, this vol., p. 1862).

Condensation of ω-aminoacetophenone with α-bromopropionyl bromide gave *ω-(α-bromopropionamido)acetophenone* (II; R = Ph, R′ = H, R″ = Me) which, on treatment with ammonia, yielded *2-propionamido-3 : 6-diphenylpyrazine*, alkaline hydrolysis of which yielded *2-amino-3 : 6-diphenylpyrazine*. The ultra-violet absorption spectra of the 2-propionamidopyrazines and the corresponding aminopyrazines described in this paper are shown in the table.

This remarkable cyclisation reaction appears to be of general application. Whilst, as mentioned previously, the inability of an α-bromoacyl derivative of a 2-amino-ketone of the type R·CO·CHR·NH_2 to yield a 2-acylamido-3 : 6-disubstituted pyrazine is readily understood, it is difficult to suggest a reason for the obvious reluctance of α-bromoacylamidomethyl ketones to yield 2-hydroxy-3 : 5-disubstituted pyrazines. Methods for the synthesis of the latter class of pyrazine derivative are being examined.

Ultra-violet absorption spectra.

	Maxima, A.	ε, max.
1. 2-Propionamido-3 : 6-dimethylpyrazine	(1) 2260; 2805	6,400; 6,800
	(2) 2250; 2810	6,000; 6,500
2. 2-Propionamido-3 : 6-diethylpyrazine	(1) 2260; 2790	6,100; 6,600
	(2) 2250; 2800	5,800; 6,000
3. 2-Propionamido-3 : 6-diphenylpyrazine	(1) 2780; 3295	13,200; 16,800
	(2) 2770; 3290	12,600; 16,000
4. 2-Amino-3 : 6-dimethylpyrazine	(3) 2340; 3190	12,000; 7,500
	(4) 2350; 3195	11,500; 7,300
5. 2-Amino-3 : 6-diethylpyrazine	(4) 2360; 3190	12,200; 8,000
6. 2-Amino-3 : 6-diphenylpyrazine	(4) 2640; 3560	12,500; 24,000

(1) Specimen obtained by the action of ammonia on a bromopropionamido-ketone.
(2) Specimen obtained by propionylation of the corresponding aminopyrazine.
(3) Specimen prepared as described by Baxter, Newbold, and Spring, *loc. cit.*
(4) Specimen obtained by hydrolysis of corresponding propionyl derivative (1).

Experimental.

α-Bromopropionamidoacetone.—A suspension of aminoacetone hydrochloride (11 g.) in dry chloroform (35 c.c.) was treated with a solution of α-bromopropionyl bromide (27 g.) in dry chloroform (25 c.c.). The mixture was cooled in ice and treated dropwise during 15 minutes with a solution of *N*-methylmorpholine (23 g.) in dry chloroform (30 c.c.), the mixture being vigorously stirred. Stirring was continued at 0° for 15 minutes, and during the next hour the mixture was allowed to attain room temperature. After being washed with water, dilute hydrochloric acid, saturated aqueous sodium carbonate, and water, the chloroform solution was dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a crystalline residue, m. p. 74—77° (14·1 g.), which was washed with light petroleum (b. p. 40—60°). Recrystallisation from benzene–light petroleum (b. p. 40—60°) gave *α-bromopropionamidoacetone* as needles, m. p. 80° (Found: C, 34·7; H, 4·7; N, 6·5. $C_6H_{10}O_2NBr$ requires C, 34·6; H, 4·8; N, 6·7%).

α-Bromopropionamidomethyl ethyl ketone was obtained in 63% yield by the same procedure from 1-aminobutan-2-one hydrochloride and α-bromopropionyl bromide. It separated from benzene–light

petroleum (b. p. 40—60°) as needles, m. p. 77° (Found : C, 37·9; H, 5·3; N, 6·3. $C_7H_{12}O_2NBr$ requires C, 37·8; H, 5·4; N, 6·3%).

ω-(α-Bromopropionamido)acetophenone was obtained in 66% yield from ω-aminoacetophenone hydrochloride and α-bromopropionyl bromide. It separated as needles, m. p. 90°, from benzene–light petroleum (b. p. 40—60°) (Found : C, 48·6; H, 4·75; N, 5·5; Br, 30·2. $C_{11}H_{12}O_2NBr$ requires C, 48·9; H, 4·4; N, 5·2; Br, 29·6%).

2-Propionamido-3 : 6-dimethylpyrazine.—A solution of α-bromopropionamidoacetone (2·6 g.) and ammonium iodide (0·5 g.) in liquid ammonia (50 c.c.) was kept at room temperature in an autoclave for 16 hours. After evaporation of the ammonia, the residue was extracted with boiling benzene (4 × 25 c.c.). The solution was filtered through a column of alumina (75 × 16 mm.), and the column washed with benzene (250 c.c.). Removal of the solvent from the filtrate yielded a colourless crystalline residue, recrystallisation of which from benzene–light petroleum (b. p. 40—60°) gave *2-propionamido-3 : 6-dimethylpyrazine* (0·9 g.) as blades, m. p. 106—108°; it is very soluble in water and in the common alcohols and is extracted by ether from an aqueous alkaline solution. For analysis, it was sublimed at 100°/0·005 mm. (Found : C, 60·6, 60·6; H, 7·4, 7·2; N, 23·3, 23·2. $C_9H_{13}ON_3$ requires C, 60·3; H, 7·2; N, 23·5%).

2-Amino-3 : 6-dimethylpyrazine.—2-Propionamido-3 : 6-dimethylpyrazine (0·2 g.) was heated under reflux for 4 hours with 10% aqueous potassium hydroxide (4 c.c.). The solution was exactly neutralised with 10% hydrochloric acid, and the mixture evaporated to dryness under reduced pressure. The residue was extracted with boiling benzene, and the dried extract evaporated to dryness. The crystalline solid was recrystallised from benzene, from which 2-amino-3 : 6-dimethylpyrazine separated as needles, m. p. 111°, showing no depression when mixed with a specimen prepared by the method of Joiner and Spoerri (*J. Amer. Chem. Soc.*, 1941, **63**, 1929). For analysis, a specimen was sublimed at 70°/1 mm. (Found : C, 55·0; H, 7·6; N, 31·6. $C_6H_9N_3,\frac{1}{2}H_2O$ requires C, 54·6; H, 7·6; N, 31·8%).

The picrate separated from ethanol as needles, m. p. 205°, either alone or when mixed with a specimen prepared from authentic 2-amino-3 : 6-dimethylpyrazine. Tschitschibabin and Shukina (*J. Russ. Phys. Chem. Soc.*, 1930, **62**, 1189) give m. p. 205° for the picrate of 2-amino-3 : 6-dimethylpyrazine.

2-Amino-3 : 6-dimethylpyrazine (0·22 g.) was heated to 90° with propionic anhydride (5 c.c.) for 15 minutes. The solution was poured into water, and the excess propionic anhydride decomposed by warming the mixture. The mixture was neutralised by addition of aqueous sodium hydrogen carbonate and evaporated to dryness under reduced pressure. The residual solid was extracted with boiling benzene (3 × 10 c.c.), the filtered extract evaporated to dryness, and the residue crystallised from benzene, from which 2-propionamido-3 : 6-dimethylpyrazine (0·2 g.) separated as needles, m. p. 107° either alone or when mixed with the specimen described above; a mixture with 2-amino-3 : 6-dimethyl pyrazine had m. p. 98—100°. 2-Hydroxy-3 : 6-dimethylpyrazine (60% yield), m. p. and mixed m. p. 211°, was obtained from this specimen of 2-amino-3 : 6-dimethylpyrazine by using the method described by Baxter, Newbold, and Spring (*loc. cit.*).

2-Propionamido-3 : 6-diethylpyrazine.—Treatment of α-bromopropionamidomethyl ethyl ketone with liquid ammonia was carried out as described in the preparation of the dimethyl homologue with the difference that the filtration of the benzene extract through a column of alumina was omitted. The benzene extract was evaporated to dryness, and the solid crystallised from benzene–light petroleum (b. p. 40—60°), from which *2-propionamido-3 : 6-diethylpyrazine* separated as needles (yield 62%), m. p. 98°; it was soluble in water and most organic solvents and sublimed readily at 70°/0·5 mm. (Found : C, 63·9, 64·1; H, 8·0, 8·0. $C_{11}H_{17}ON_3$ requires C, 63·8; H, 8·2%).

2-Amino-3 : 6-diethylpyrazine.—A solution of 2-propionamido-3 : 6-diethylpyrazine (0·2 g.) in N-sodium hydroxide solution (10 c.c.) was heated under reflux. After 1 hour, an oil began to separate, and after 3 hours the mixture was cooled, whereupon the oil crystallised. The solid was isolated by means of ether, evaporation of the dried ethereal solution giving *2-amino-3 : 5-diethylpyrazine* as long needles, m. p. 42°. It is extremely soluble in water and the common organic solvents and this property precluded efficient crystallisation. For analysis, it was sublimed at 35°/10^{-4} mm., being obtained as hygroscopic needles, m. p. 42° (Found : C, 60·2, 60·5; H, 8·2, 8·8; N, 25·9, 26·0. $C_8H_{13}N_3,\frac{1}{2}H_2O$ requires C, 60·0; H, 8·7; N, 26·2%). Its *picrate* separated as needles from ethanol, m. p. 157° (Found : C, 44·7; H, 4·2; N, 22·2. $C_{14}H_{16}O_7N_6$ requires C, 44·4; H, 4·2; N, 22·1%).

A mixture of 2-amino-3 : 6-diethylpyrazine (0·2 g.) and propionic anhydride (5 c.c.) was kept at 90° for 15 minutes, solution then being complete. The cold solution was treated with water (10 c.c.), and the mixture warmed on the steam-bath to decompose the excess of anhydride. The mixture was neutralised by the addition of sodium hydrogen carbonate and evaporated to dryness under reduced pressure. The residue was extracted with boiling benzene, and the dried extract evaporated to dryness. The crystalline residue was recrystallised from benzene–light petroleum (b. p. 40—60°), from which *2-propionamido-3 : 6-diethylpyrazine* (0·2 g.) separated as needles, m. p. 98° not depressed when mixed with the specimen prepared as described above (Found : N, 20·3. $C_{11}H_{17}ON_3$ requires N, 20·3%).

2-Hydroxy-3 : 6-diethylpyrazine.—A solution of 2-amino-3 : 6-diethylpyrazine (0·2 g.) in N-hydrochloric acid (10 c.c.) at 0° was treated with sodium nitrite (0·2 g.) added in small quantities during 10 minutes with stirring. The solution was kept at 0° for 15 minutes and then allowed to attain room temperature, kept at this temperature for 3 hours, neutralised with sodium hydrogen carbonate, and extracted with chloroform. The dried (Na_2SO_4) extract was evaporated, and the crystalline residue recrystallised from light petroleum, from which *2-hydroxy-3 : 6-diethylpyrazine* (0·1 g.) separated in needles, m. p. 135°. Light absorption in alcohol : Maxima at 2270 A., $\epsilon = 6800$, and 3220 A., $\epsilon = 8100$. For analysis, it was sublimed at 100°/10^{-3} mm. (Found : C, 63·7; H, 8·0; N, 18·2. $C_8H_{12}ON_2$ requires C, 63·2; H, 7·9; N, 18·4%).

2-Propionamido-3 : 6-diphenylpyrazine.—ω-(α-Bromopropionamido)acetophenone was treated with liquid ammonia as described for the preparation of 2-propionamido-3 : 6-dimethylpyrazine. After evaporation of the ammonia, the solid residue was extracted with boiling chloroform. The dried extract was evaporated, and the residue crystallised from ethanol, from which *2-propionamido-3 : 6-diphenylpyrazine* separated as needles, m. p. 212·5°; yield 60%. It sublimed readily at 120°/10^{-3} mm. and was

insoluble in water and aqueous sodium hydroxide solution (Found: C, 75·0; H, 5·7; N, 14·0, 14·1. $C_{19}H_{17}ON_3$ requires C, 75·2; H, 5·6; N, 13·9%).

2-Amino-3 : 6-diphenylpyrazine.—A suspension of 2-propionamido-3 : 6-diphenylpyrazine (3·0 g.) in N-sodium hydroxide solution (25 c.c.) and ethanol (0·5 c.c.) was refluxed for 5 hours. The mixture was cooled, and the yellow solid collected. Crystallisation from ethanol gave *2-amino-3 : 6-diphenylpyrazine* as yellow plates, m. p. 186°; yield 90%. Solutions of this base in the common organic solvents show a blue fluorescence. It was only weakly basic, solutions in concentrated hydrochloric acid depositing an orange-coloured hydrochloride which is decomposed by water with regeneration of the parent base. 2-Amino-3 : 6-diphenylpyrazine gave a positive carbylamine reaction; it did not yield a picrate under normal reaction conditions (Found: C, 78·0; H, 5·2; N, 16·8. $C_{16}H_{13}N_3$ requires C, 77·7; H, 5·3; N, 17·0%).

Treatment of 2-amino-3 : 6-diphenylpyrazine with propionic anhydride as described in the case of the diethyl homologue gave 2-propionamido-3 : 6-diphenylpyrazine as needles from ethanol, m. p. 212·5°, not depressed when mixed with the specimen described above (yield, quantitative) (Found: C, 75·6; H, 5·6; N, 13·9%).

The *diacetyl* derivative of 2-amino-3 : 6-diphenylpyrazine was obtained by heating the base (0·2 g.) under reflux with acetic anhydride (10 c.c.) for 15 minutes. The mixture was poured on ice, and the crystalline precipitate collected and crystallised from methanol, from which the diacetyl derivative separated as needles, m. p. 117° (Found: C, 72·3; H, 5·3. $C_{20}H_{17}O_2N_3$ requires C, 72·3; H, 5·4%).

We wish to thank Imperial Chemical Industries Ltd. for grants and gifts of materials, and the Department of Scientific and Industrial Research for a Maintenance Award to one of us (W.S.).

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371. *Pyrazine Derivatives. Part VI. The Oxidation of 2-Ethoxy- and 2-Chloro-pyrazine Derivatives with Hydrogen Peroxide.*

By R. A. BAXTER, G. T. NEWBOLD, and F. S. SPRING.

In a preliminary study of possible methods for the synthesis of aspergillic acid, a cyclic hydroxamic acid related to pyrazine, the oxidation of some pyrazine derivatives has been investigated. Oxidation of 2-chloro-3 : 6-dimethylpyrazine (VII) with hydrogen peroxide gives the corresponding 4-oxide (VIII) and similar oxidation of 2-ethoxy-3 : 6-dimethylpyrazine (X) gives the 4-oxide (IX). Oxidation at the 1-position does not occur and the 4-oxides resist oxidation at the 1-position. An interesting case of side-chain halogenation was observed, treatment of 2-ethoxy-3 : 6-dimethylpyrazine 4-oxide (IX) with phosphoryl chloride yielding 2-ethoxy-6-methyl-3-chloromethylpyrazine (XI).

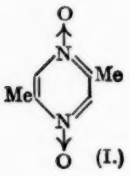
IN Part IV (*J.*, 1947, 1183), we described the preparation of 2 : 5-dimethylpyrazine 1-oxide (VI) and 2 : 5-dimethylpyrazine 1 : 4-dioxide (I) and we showed that, when treated with phosphoryl chloride, they are converted into 2-chloro- (VII) and 2 : 5-dichloro-3 : 6-dimethylpyrazine (II), respectively. In Part III (*J.*, 1947, 1179) we showed that the mono- and di-chloro-3 : 6-dimethylpyrazines can be obtained by treatment of alanine anhydride with phosphoryl chloride.

An examination of the oxidation of 2-chloro- and 2-ethoxy-3 : 6-dimethylpyrazine was undertaken in the hope that a method might thereby be developed for the synthesis of a cyclic hydroxamic acid related to aspergillic acid (Newbold and Spring, *J.*, 1947, 373). Treatment of 2-chloro-3 : 6-dimethylpyrazine (VII) with hydrogen peroxide gives *2-chloro-3 : 6-dimethylpyrazine 4-oxide* (VIII) and not the 1-oxide. Treatment of the 4-oxide with phosphoryl chloride yields 2 : 5-dichloro-3 : 6-dimethylpyrazine (II). The 4-oxide (VIII) is smoothly converted into *2-ethoxy-3 : 6-dimethylpyrazine 4-oxide* (IX) when treated with sodium ethoxide. The 2-ethoxy-4-oxide (IX) is also obtained by oxidation of 2-ethoxy-3 : 6-dimethylpyrazine (X) with hydrogen peroxide; when treated with mineral acid it readily gave *2-hydroxy-3 : 6-dimethylpyrazine 4-oxide* (XIII) which did not show the properties of a hydroxamic acid. Thus oxidation of a 2-chloro- or a 2-ethoxy-pyrazine derivative with hydrogen peroxide yields a 4-monoxide only, and the latter appears to resist further oxidation at the 1-position. The synthesis of a pyrazine cyclic hydroxamic acid by a direct oxidation of a 2-substituted pyrazine appears to be impracticable.

Reaction of 2-ethoxy-3 : 6-dimethylpyrazine 4-oxide (IX) with phosphoryl chloride yields a mixture of two products, easily separable by virtue of their different basicities. The non-basic component was identified as the expected *2-chloro-5-ethoxy-3 : 6-dimethylpyrazine* (III). This compound is also obtained by treatment of 2 : 5-dichloro-3 : 6-dimethylpyrazine with sodium ethoxide using relatively mild reaction conditions, and on hydrolysis with dilute sulphuric acid it yields 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine (IV).

The second product of the reaction between 2-ethoxy-3 : 6-dimethylpyrazine 4-oxide and phosphoryl chloride is *2-ethoxy-6-methyl-3-chloromethylpyrazine* (XI), characterised by the

formation of a crystalline *hydrochloride*. When treated with sodium ethoxide it gives 2-*ethoxy*-6-*methyl*-3-*ethoxymethylpyrazine* (XII) and on hydrolysis with potassium hydroxide solution 2-*ethoxy*-6-*methyl*-3-*hydroxymethylpyrazine* is obtained. Attempted acid hydrolysis of 2-ethoxy-6-methyl-3-chloromethylpyrazine (XI) and of 2-ethoxy-6-methyl-3-ethoxymethylpyrazine (XII) was unsuccessful. The ultra-violet absorption spectra of (XI), (XII), and 2-ethoxy-6-methyl-3-hydroxymethylpyrazine are very similar to that of 2-ethoxy-3 : 6-dimethylpyrazine (see table). The substitution of hydrogen by halogen in a side chain of a heterocyclic compound *via* a *N*-oxide has previously been observed in the case of a quinoxaline *N*-oxide derivative (Newbold and Spring, this vol., p. 519), and we intend to determine whether this reaction is of general applicability.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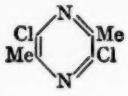
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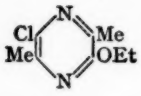
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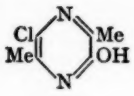
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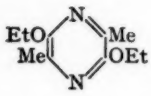
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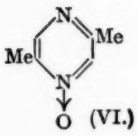
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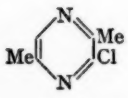
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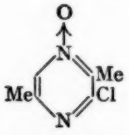
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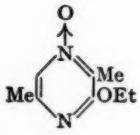
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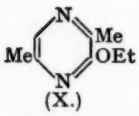
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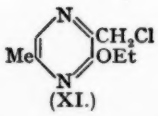
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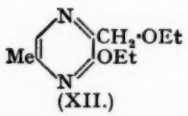
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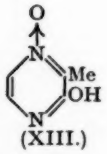
(XIII.)

The experiments described below were undertaken with the object of preparing a 2 : 5-dihydroxypyrazine derivative which was required in connection with an examination of a substance, $C_{12}H_{20}O_3N_2$, obtained together with aspergillic acid from culture filtrates of *Aspergillus flavus* (Menzel, Wintersteiner, and Rake, *J. Bact.*, 1943, **46**, 109). Such a 2 : 5-dihydroxypyrazine derivative would be of interest in that it is the simplest oxidation product of a diketopiperazine. Treatment of either 2-chloro-5-ethoxy-3 : 6-dimethylpyrazine (III) or 2 : 5-dichloro-3 : 6-dimethylpyrazine (II) with sodium ethoxide yields 2 : 5-*diethoxy*-3 : 6-*dimethylpyrazine* (V), which was recovered unchanged after prolonged heating with mineral acids. We have previously reported that drastic alkaline hydrolysis of 2 : 5-dichloro-3 : 6-dimethylpyrazine gives 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine and not the 2 : 5-dihydroxy-derivative, and that fusion of 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine with alkali gives 2-hydroxy-3 : 6-dimethylpyrazine.

In an alternative attempt to prepare 2 : 5-dihydroxy-3 : 6-dimethylpyrazine, we were

Absorption spectra.

(All determinations in ethanol solution.)

	Maxima A.	ε.
2-Chloro-5-ethoxy-3 : 6-dimethylpyrazine (III)	3040	9,200
2 : 5-Diethoxy-3 : 6-dimethylpyrazine (V)	3180	10,600
2-Ethoxy-3 : 6-dimethylpyrazine (X)	2980	8,400
2-Ethoxy-6-methyl-3-chloromethylpyrazine (XI)	2980	8,800
2-Ethoxy-6-methyl-3-ethoxymethylpyrazine (XII)	2970	8,400
2-Ethoxy-6-methyl-3-hydroxymethylpyrazine	2950	7,100
2-Hydroxy-3 : 6-dimethylpyrazine 4-oxide (XIII)	2250	15,200
	2720	6,200
	3270	4,800

unable to convert 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine into 2-hydroxy-5-ethoxy-3 : 6-dimethylpyrazine. Whilst treatment of 2-chloro-5-ethoxy-3 : 6-dimethylpyrazine with dilute sulphuric acid yields 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine, hydrolysis with concentrated

hydrochloric acid leads to rupture of the pyrazine ring and formation of DL-alanine. 2-Hydroxy-3 : 6-dimethylpyrazine couples with benzenediazonium chloride in alkaline solution to give 2-hydroxy-5-phenylazo-3 : 6-dimethylpyrazine (Gastaldi and Princevalle, *Gazzetta*, 1928, **58**, 679). When treated with sodium hydrosulphite (dithionite), this gives *2-amino-5-hydroxy-3 : 6-dimethylpyrazine*, but attempts to convert this into 2 : 5-dihydroxy-3 : 6-dimethylpyrazine with nitrous acid were unsuccessful.

EXPERIMENTAL.

2-Chloro-3 : 6-dimethylpyrazine 4-Oxide.—A solution of 2-chloro-3 : 6-dimethylpyrazine (2·25 g.) in glacial acetic acid (10 c.c.) was treated with hydrogen peroxide (100-vol., 20 c.c.) and kept at 56° for 16 hours. The reaction mixture was concentrated (reduced pressure) and made alkaline by the addition of 20% potassium hydroxide solution. The solid was isolated by means of chloroform and crystallised from benzene–light petroleum (b. p. 60—80°), from which *2-chloro-3 : 6-dimethylpyrazine 4-oxide* separated as needles, m. p. 113—115° (yield 65%). For analysis, it was sublimed at 100°/0·5 mm. (Found : C, 45·7; H, 4·2. $C_6H_7ON_2Cl$ requires C, 45·4; H, 4·4%).

2 : 5-Dichloro-3 : 6-dimethylpyrazine.—2-Chloro-3 : 6-dimethylpyrazine 4-oxide (0·6 g.) was added to phosphoryl chloride (6 c.c.), and the mixture heated under reflux for 15 minutes, then concentrated to one-third bulk and poured on crushed ice. After standing, the solid was collected and purified by sublimation at 70°/0·5 mm., 2 : 5-dichloro-3 : 6-dimethylpyrazine (0·2 g.) being obtained as needles, m. p. 70° either alone or when mixed with an authentic specimen.

2-Ethoxy-3 : 6-dimethylpyrazine 4-Oxide.—(*a*) A solution of 2-chloro-3 : 6-dimethylpyrazine 4-oxide (0·3 g.) in dry ethanol was added to one of sodium ethoxide in ethanol (from 0·25 g. of sodium and 10 c.c. of ethanol), and the mixture heated under reflux for 5 hours. The product isolated in the usual manner was purified by sublimation at 90°/0·5 mm., *2-ethoxy-3 : 6-dimethylpyrazine 4-oxide* being obtained as needles, m. p. 92—94° (Found : C, 56·9; H, 6·8; N, 16·5. $C_8H_{12}O_2N_2$ requires C, 57·1; H, 7·1; N, 16·7%).

(*b*) A solution of 2-ethoxy-3 : 6-dimethylpyrazine (2·5 g.) in acetic acid (10 c.c.) was oxidised with hydrogen peroxide, the method described above being used. The oxide (2·55 g.) was obtained as needles, m. p. 92—94° either alone or when mixed with a specimen obtained by method (*a*).

2-Hydroxy-3 : 6-dimethylpyrazine 4-Oxide.—2-Ethoxy-3 : 6-dimethylpyrazine-4-oxide (0·5 g.) in hydrochloric acid (10 c.c.; 3N) was heated under reflux for 3 hours. The solution was concentrated (reduced pressure), and the solid (210 mg.) collected. Crystallisation from ethanol (charcoal) gave *2-hydroxy-3 : 6-dimethylpyrazine 4-oxide* as prismatic needles which decomposed above 250°; for analysis it was sublimed at 190°/0·001 mm. It does not give a colour with ferric chloride and does not exhibit acidic properties (Found : C, 51·7; H, 6·0. $C_6H_8O_2N_2$ requires C, 51·4; H, 5·7%).

2-Chloro-5-ethoxy-3 : 6-dimethylpyrazine.—(*a*) A solution of 2 : 5-dichloro-3 : 6-dimethylpyrazine (2 g.) in ethanolic sodium ethoxide (from 1 g. of sodium and 25 c.c. of ethanol) was refluxed for 8 hours. The excess of alcohol was removed by distillation, and the residue diluted with water (50 c.c.) and extracted with ether. The dried (Na_2SO_4) extract was evaporated, the oily product (1·6 g.) solidifying on standing. *2-Chloro-5-ethoxy-3 : 6-dimethylpyrazine*, b. p. 65°/1 mm., was purified by sublimation, being obtained as needles, m. p. 30° (Found : C, 51·7; H, 5·9. $C_8H_{11}ON_2Cl$ requires C, 51·5; H, 5·9%).

(*b*) 2-Ethoxy-3 : 6-dimethylpyrazine 4-oxide (2·5 g.) was added to phosphoryl chloride (15 c.c.), and the mixture gradually heated and finally refluxed for 10 minutes. The cooled reaction mixture was poured on ice (100 g.) and stirred, the temperature being kept below 5°. The solid was filtered off (filtrate A), and after drying was purified by sublimation at 30°/10^{-4} mm., 2-chloro-5-ethoxy-3 : 6-dimethylpyrazine being obtained as needles (0·93 g.), m. p. 30° either alone or when mixed with the specimen obtained by method (*a*).

2-Chloro-5-hydroxy-3 : 6-dimethylpyrazine.—2-Chloro-5-ethoxy-3 : 6-dimethylpyrazine (0·25 g.) was heated for 16 hours with 6N-sulphuric acid (10 c.c.). The cold solution was extracted with ether, and the dried extract evaporated, 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine being obtained; after crystallisation from ethanol, it formed needles, m. p. 222—224° not depressed by an authentic specimen (Part III, *loc. cit.*).

DL-*Alanine.*—A solution of 2-chloro-5-ethoxy-3 : 6-dimethylpyrazine (1 g.) in ethanol (5 c.c.) and concentrated hydrochloric acid (15 c.c.) was refluxed for 16 hours. The solution was evaporated to dryness, and a crystalline solid was obtained which was very soluble in water, the solution giving an acid reaction. An excess of an ammoniacal solution of silver nitrate was added to an aqueous solution of the solid, and the precipitated silver chloride and oxide removed by filtration. The filtrate was treated with hydrogen sulphide and the precipitated silver sulphide removed by filtration. Evaporation of the solution yielded a crystalline solid which, after recrystallisation from water, yielded DL-alanine as needles, m. p. 274—276° either alone or when mixed with an authentic specimen (Found: C, 40·8; H, 7·75. Calc. for $C_3H_7O_2N$: C, 40·45; H, 7·9%).

2-Ethoxy-6-methyl-3-chloromethylpyrazine.—The filtrate A (above) was neutralised by addition of solid sodium carbonate and extracted with ether. The dried (Na_2SO_4) extract was evaporated, and the residual oil distilled to give a colourless mobile oil (1·2 g.), b. p. 65°/0·5 mm. Redistillation gave *2-ethoxy-6-methyl-3-chloromethylpyrazine* as a colourless oil, b. p. 106°/10 mm., $n_D^{18°}$ 1·5235 (Found : C, 51·7; H, 6·1. $C_8H_{11}ON_2Cl$ requires C, 51·5; H, 5·9%). The *hydrochloride*, obtained by passing dry hydrogen chloride into a dry ethereal solution of the base, separated as colourless needles, which, after sublimation at 100°/0·5 mm., had m. p. 115°. It is decomposed by water with regeneration of the base (Found : C, 43·3; H, 5·3. $C_8H_{11}ON_2Cl,HCl$ requires C, 43·05; H, 5·4%).

2-Ethoxy-6-methyl-3-ethoxymethylpyrazine.—2-Ethoxy-6-methyl-3-chloromethylpyrazine (0·6 g.) was treated with ethanolic sodium ethoxide (from 0·4 g. of sodium and 15 c.c. of ethanol), and the mixture heated in a sealed tube for 6 hours at 130—135°. The reaction product was isolated by means of ether,

and after distillation gave 2-*ethoxy*-6-*methyl*-3-*ethoxymethylpyrazine* as a colourless oil (0·5 g.), b. p. 112°/10 mm., $n_D^{18°}$ 1·4950 (Found: C, 61·6; H, 8·1. $C_{10}H_{16}O_2N_2$ requires C, 61·2; H, 8·2%). The *chloroplatinate* separated from methanol as orange-coloured prismatic needles, m. p. 170° (decomp.) [Found: Pt, 24·5, 24·35. $(C_{10}H_{16}O_2N_2)_2,H_2PtCl_6$ requires Pt, 24·3%].

2 : 5-*Diethoxy*-3 : 6-*dimethylpyrazine*.—A solution of 2-chloro-5-ethoxy-3 : 6-dimethylpyrazine (0·45 g.) in ethanolic sodium ethoxide (from 0·5 g. of sodium and 10 c.c. of ethanol) was heated in a sealed tube at 140° for 12 hours. The ethanol was removed by distillation, and the residue treated with water. The solid (0·3 g.) which separated as blades, m. p. 75—78°, was purified by sublimation at 70°/0·01 mm., 2 : 5-*diethoxy*-3 : 6-*dimethylpyrazine* being obtained as a crystalline mass, m. p. 79—80°. This base was also obtained in 60% yield by heating 2 : 5-dichloro-3 : 6-dimethylpyrazine with ethanolic sodium ethoxide for 8 hours at 150° (Found: C, 61·3; H, 8·3. $C_{10}H_{16}O_2N_2$ requires C, 61·2; H, 8·2%).

2-*Ethoxy*-6-*methyl*-3-*hydroxymethylpyrazine*.—2-Ethoxy-6-methyl-3-chloromethylpyrazine (1·0 g.) in dioxan (2 c.c.) was heated under reflux with potassium hydroxide solution (20%; 5 c.c.) for 14 hours. The cooled mixture was extracted with ether, and the dried (Na_2SO_4) extract evaporated. The residue was distilled at 0·001 mm.; the fraction distilling at a bath temperature of 100° (200 mg.) solidified on standing. Crystallisation from light petroleum (b. p. 60—80°) at −20°, followed by sublimation at 40°/0·0001 mm., gave 2-*ethoxy*-6-*methyl*-3-*hydroxymethylpyrazine* as needles, m. p. 45—46°. It is very soluble in water and the common organic solvents (Found: C, 57·45; H, 7·4. $C_8H_{12}O_2N_2$ requires C, 57·1; H, 7·1%).

2-*Amino*-5-*hydroxy*-3 : 6-*dimethylpyrazine*.—A suspension of 2-hydroxy-5-phenylazo-3 : 6-dimethylpyrazine (0·15 g.) in sodium hydroxide solution (2N; 10 c.c.) was treated with sodium hydrosulphite (dithionite) (0·6 g.), and the mixture boiled. When solution was complete, the mixture was evaporated to half bulk under reduced pressure, acidified with acetic acid, and evaporated to dryness. The residue was dried in a vacuum over phosphoric oxide and then extracted with benzene (Soxhlet). Concentration of the benzene extract gave 2-*amino*-5-*hydroxy*-3 : 6-*dimethylpyrazine* which, after two recrystallisations from ethanol–benzene, separated as small yellow needles, m. p. 225—230° (decomp.) (Found: C, 51·9; H, 6·6; N, 29·7. $C_6H_9ON_3$ requires C, 51·8; H, 6·5; N, 30·2%).

We wish to thank the Department of Scientific and Industrial Research for grants.

THE ROYAL TECHNICAL COLLEGE, GLASGOW, C.1. [*Received, December 29th*, 1947.]

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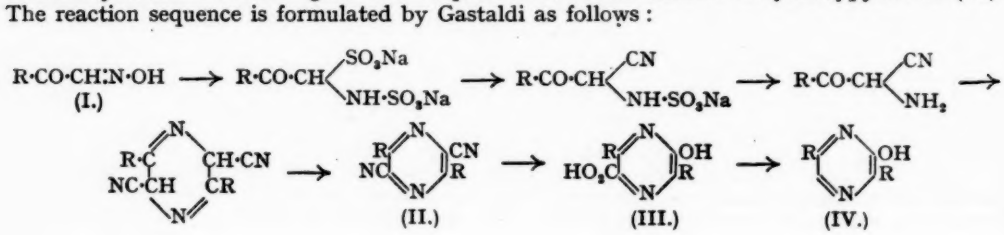
372. *Pyrazine Derivatives. Part VII. The Preparation of Hydroxypyrazine Derivatives by Gastaldi's Method.*

By WILLIAM SHARP and F. S. SPRING.

Oximinomethyl ethyl ketone has been converted into 2 : 5-*dicyano*-3 : 6-*diethylpyrazine*. Alkaline hydrolysis of the dicyano-compound gives 2-*hydroxy*-3 : 6-*diethylpyrazine*-5-*carboxylic acid*, decarboxylation of which yields 2-hydroxy-3 : 6-diethylpyrazine.

Two methods for the synthesis of alkylhydroxypyrazine derivatives had been reported when this series of investigations commenced. The first is due to Gastaldi (*Gazzetta*, 1921, **51**, I, 233) and the second to Tota and Elderfield (*J. Org. Chem.*, 1942, **7**, 317). Several methods for the synthesis of hydroxypyrazines have subsequently been described in this series (Baxter, Newbold, and Spring, *J.*, 1947, 370; Newbold and Spring, *J.*, 1947, 1183; Baxter and Spring, *J.*, 1947, 1179), and in addition Tota and Elderfield's method, which is limited to the preparation of 5 : 6-disubstituted and 3 : 5 : 6-trisubstituted 2-hydroxypyrazines, has been modified to yield a 2-hydroxy-3 : 6-dialkylpyrazine (Baxter, Newbold, and Spring, *loc. cit.*). Gastaldi's method was of particular interest to us since it gave a 3 : 6-disubstituted 2-hydroxypyrazine, and the primary object of our study was the synthesis of 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (cf. Newbold and Spring, *J.*, 1947, 373). The method consists in the treatment of the bisulphite compound of an oximinoketone with potassium cyanide, followed by heating the reaction product with hydrochloric acid, whereby a 2 : 5-dicyano-3 : 6-disubstituted pyrazine (II) is obtained. When heated with alkali, the dicyano-compound (II) undergoes a remarkable hydrolytic reaction to yield a 3 : 6-disubstituted 2-hydroxypyrazine-5-carboxylic acid (III), decarboxylation of which gives the required 3 : 6-disubstituted 2-hydroxypyrazine (IV). The reaction sequence is formulated by Gastaldi as follows:



Gastaldi applied the method to oximinoacetone and oximinoacetophenone. We have extended the method to *oximinomethyl ethyl ketone* (I; R = Et), obtained by the action of nitrous acid on sodium propionylacetate. The bisulphite compound of the oximino-ketone was treated with potassium cyanide, and the reaction mixture heated with hydrochloric acid, whereby 2 : 5-*dicyano*-3 : 6-*diethylpyrazine* (II; R = Et) was obtained. Hydrolysis of the dicyano-compound with alkali gave 2-*hydroxy*-3 : 6-*diethylpyrazine*-5-*carboxylic acid* (III; R = Et), which on heating yielded 2-hydroxy-3 : 6-diethylpyrazine (IV; R = Et) identical with the specimen obtained by Newbold, Spring, and Sweeny (Part V, this vol., p. 1855) from 2-amino-3 : 6-diethylpyrazine.

The formation of 2 : 5-dicyano-3 : 6-dimethylpyrazine (II; R = Me) from oximinoacetone has been reinvestigated and conditions are described in the experimental section whereby a 46% yield of the dicyano-derivative can be obtained. For comparison purposes, 2 : 5-dicyano-3 : 6-dimethylpyrazine was obtained from ethyl 3 : 6-dimethylpyrazine-2 : 5-dicarboxylate (Wleügel, *Ber.*, 1882, **15**, 1051; Gabriel and Posner, *Ber.*, 1894, **27**, 1141; Kalischer, *Ber.*, 1895, **28**, 1518; Cerchez and Colesiu, *Bull. Soc. chim.*, 1931, **49**, 1291; Adkins and Reeve, *J. Amer. Chem. Soc.*, 1938, **60**, 1328). The ester was converted into the corresponding diamide, which on dehydration yielded 2 : 5-dicyano-3 : 6-dimethylpyrazine identical with the specimen obtained by Gastaldi's method.

The remarkable behaviour of 2 : 5-dicyanopyrazine derivatives when treated with alkali proceeds under relatively mild reaction conditions; thus, when a solution of 2 : 5-dicyano-3 : 6-dimethylpyrazine is warmed for 2 minutes with 1% aqueous potassium hydroxide the presence of potassium cyanide is readily detected.

Experimental.

Oximinomethyl Ethyl Ketone.—Ethyl propionylacetate (40 g., b. p. 185—196°), obtained in 56% yield from ethyl cyanoacetate by Blaise's method (*Compt. rend.*, 1901, **132**, 978; Willstätter and Clarke, *Ber.*, 1914, **47**, 298), was added to a solution of sodium hydroxide (2·4%; 600 c.c.), and the mixture kept at room temperature for 24 hours. A solution of sodium nitrite (21 g.) in water (80 c.c.) was added, and the mixture treated at 5° with sulphuric acid (20%; 172 g.), added slowly with stirring. After the addition of ice and sodium hydroxide solution (40%; 40 c.c.), the mixture was extracted with ether. The aqueous solution was acidified with sulphuric acid (20%) at 5° and kept at this temperature for 1 hour. The mixture was extracted with ether (6 × 150 c.c.), the extract dried ($CaCl_2$), and the solvent removed. The residual oil crystallised (15·7 g.), and on recrystallisation (charcoal) from light petroleum (b. p. 60—80°) gave *oximinomethyl ethyl ketone* in hygroscopic needles, m. p. 55°; it has an odour similar to that of oximinoacetone (Found: C, 47·1; H, 6·9; N, 14·2. $C_4H_7O_2N$ requires C, 47·5; H, 6·9; N, 13·9%).

2 : 5-*Dicyano*-3 : 6-*diethylpyrazine.*—Oximinomethyl ethyl ketone (40 g.) was gradually added with shaking to a solution of sodium metabisulphite (183 g.) in water (317 c.c.) saturated with sulphur dioxide. The solution, which became warm during the addition, was kept overnight at room temperature. Alcohol (1500 c.c.) containing acetic acid (7·5 c.c.) was added gradually with shaking, and the precipitated solid collected next day when it had become granular. A solution of the solid in water (600 c.c.) was treated with alcohol (600 c.c.), and the mixture kept overnight. The precipitated sodium hydrogen sulphite was removed, and the filtrate diluted with alcohol (3000 c.c.) and kept overnight. The separated crude bisulphite compound of oximinomethyl ethyl ketone (126 g.; theoretical yield 115 g.) was collected and washed with alcohol; although contaminated with sodium hydrogen sulphite it was not further purified. A solution of the bisulphite compound (50 g.) in water (100 c.c.) was treated with potassium cyanide (22 g.) which was added slowly with shaking, and the solution kept at 45—50° for 5 hours, during which time the colour changed to yellow, through orange to red, and finally to brown. Hydrochloric acid (20%; 27 c.c.) was added, and the mixture heated at 55—60° for 1 hour. Concentrated hydrochloric acid (45 c.c.) was added slowly with stirring, and the solution kept at 55—60° for 24 hours during which time a crystalline solid separated. The mixture was cooled, and the solid collected, washed with water, dried, and extracted with boiling alcohol. On concentration and cooling the extract, a crystalline solid separated which when recrystallised (charcoal) from alcohol gave 2 : 5-*dicyano*-3 : 6-*diethylpyrazine* (2·82 g.) as plates, m. p. 115°. It is more soluble in alcohol than the 3 : 6-dimethyl homologue and volatilises from solutions heated on the water-bath (Found: C, 64·7; H, 5·4; N, 29·7. $C_{10}H_{10}N_4$ requires C, 64·5; H, 5·4; N, 30·1%).

2-*Hydroxy*-3 : 6-*diethylpyrazine*-5-*carboxylic Acid.*—A solution of 2 : 5-dicyano-3 : 6-diethylpyrazine (0·35 g.) in potassium hydroxide solution (15%; 10 c.c.) was refluxed for 24 hours. The cold solution was acidified with dilute hydrochloric acid, whereupon the odour of hydrogen cyanide was detected and a mixture of silica and reaction product was precipitated. The reaction mixture was evaporated to dryness, and the dried residue extracted with boiling alcohol (60 c.c.). Alcohol was removed from the filtered extract, and the orange-coloured solid crystallised from benzene (charcoal) to yield 2-*hydroxy*-3 : 6-*diethylpyrazine*-5-*carboxylic acid* (0·21 g.) as small prisms, m. p. 166°. There was no sign of decarboxylation at its m. p., but brisk evolution of carbon dioxide occurred at 200° (Found: C, 55·7; H, 6·1; N, 14·7. $C_9H_{12}O_3N_2$ requires C, 55·1; H, 6·2; N, 14·3%).

2-*Hydroxy*-3 : 6-*diethylpyrazine.*—A " Pyrex " tube containing a mixture of 2-hydroxy-3 : 6-diethylpyrazine-5-carboxylic acid (0·7 g.) and powdered glass (1·4 g.) was heated rapidly by immersion in a bath at 300° for 5 minutes. The acid melted, carbon dioxide was evolved, and a crystalline solid (0·35 g.) sublimed. Resublimation at 100°/0·005 mm. gave 2-hydroxy-3 : 6-diethylpyrazine as needles, m. p. 135°,

undepressed when mixed with the specimen described in Part V (*loc. cit.*) (Found: C, 62·8; H, 7·8; N, 18·4. Calc. for $C_8H_{12}ON_2$: C, 63·2; H, 7·9; N, 18·4%).

2 : 5-*Dicyano*-3 : 6-*dimethylpyrazine*.—(*a*) Starting from oximinoacetone and using the procedure detailed above, 2 : 5-dicyano-3 : 6-dimethylpyrazine was obtained as lustrous plates, m. p. 210° (Gastaldi, *loc. cit.*, give m. p. 207°) (yield, 46%) (Found: C, 60·4; H, 3·8; N, 35·3. Calc. for $C_8H_6N_4$: C, 60·8; H, 3·8; N, 35·4%). Hydrolysis of this compound with 15% potassium hydroxide solution as described for the 3 : 6-diethyl homologue gave 2-hydroxy-3 : 6-dimethylpyrazine-5-carboxylic acid as prismatic needles from water, m. p. 268° (Gastaldi, *loc. cit.*, gives m. p. 270°) (yield, 50%). When heated with powdered glass, using the method described above, the acid was converted into 2-hydroxy-3 : 6-dimethylpyrazine, which was obtained as prismatic needles from light petroleum (b. p. 100—120°), m. p. 207—209° undepressed when mixed with an authentic specimen (yield, 77%) (Found: C, 57·8; H, 6·7. Calc. for $C_6H_8ON_2$: C, 58·1; H, 6·45%).

(*b*) * Ethyl 3 : 6-dimethylpyrazine-2 : 5-dicarboxylate (m. p. 80—83°, 3·5 g.) prepared by catalytic reduction of ethyl α-oximinoacetoacetate in ethanol solution using a Raney nickel catalyst, was dissolved in a solution of ethanol saturated at room temperature with dry ammonia and kept for 3 days. The crystalline solid was collected (2·5 g.) and recrystallised from water to yield 3 : 6-dimethylpyrazine-2 : 5-dicarboxyamide as fine needles, m. p. 297—298° (with previous darkening and some sublimation); Gastaldi and Princevalle (*Gazzetta*, 1928, **58**, 414) give m. p. 290° (Found: C, 49·6; H, 5·3. Calc. for $C_8H_{10}O_2N_4$: C, 49·5; H, 5·15%).

The diamide (5 g.) and phosphoric oxide (19 g.) were stirred in boiling toluene for 16 hours. The cold mixture was filtered and the black solid extracted with toluene (Soxhlet). Removal of the toluene under reduced pressure, followed by crystallisation of the residue from ethanol, gave 2 : 5-dicyano-3 : 6-dimethylpyrazine as glistening leaflets, m. p. 210·5—211·5°, undepressed when mixed with the specimen prepared by method (*a*) (Found: C, 60·7; H, 3·9; N, 35·4%).

Grateful acknowledgment is made to Imperial Chemical Industries Limited for grants.

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373. *Hydroxamic Acids. Part I. Cyclic Hydroxamic Acids derived from Pyridine and Quinoline.*

By G. T. NEWBOLD and F. S. SPRING.

The preparation of the cyclic hydroxamic acids 2-hydroxypyridine 1-oxide (IX) and 2-hydroxyquinoline 1-oxide (XII) is described.

ASPERGILLIC acid has been shown to have a high inhibitory *in vitro* activity against some Gram-negative and Gram-positive organisms (White, *Science*, 1940, **92**, 127; White and Hill, *J. Bact.*, 1942, **43**, 12; Jones, Rake, and Hamre, *ibid.*, 1943, **45**, 461; Menzel, Wintersteiner, and Rake, *ibid.*, 1943, **46**, 109; Dunham, Hamre, McKee, and Rake, *Proc. Soc. Exp. Biol. Med.*, 1943, **54**, 211) and against *M. tuberculosis* (Goth, *J. Lab. Clin. Med.*, 1945, **30**, 899). The toxicity of aspergillic acid is such that it is unlikely to find useful applications in the treatment of systemic infections. Aspergillic acid is a hydroxamic acid related to pyrazine, and although there is some dubiety concerning the nature of the side chains R and R′, it is correctly represented by the structure (I).†

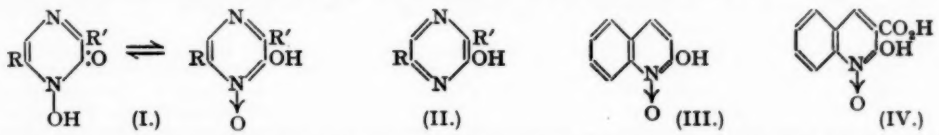
On mild reduction, aspergillic acid is converted into the hydroxypyrazine (II), deoxyaspergillic acid (Dutcher, *J. Biol. Chem.*, 1947, **171**, 321, 341; Newbold and Spring, *J.*, 1947, 373), which is relatively ineffective as an antibacterial agent. It would appear that the activity of aspergillic acid in this respect is to be attributed to the cyclic hydroxamic acid grouping. The work described in this and succeeding communications was undertaken with the object of developing methods for the synthesis of cyclic hydroxamic acids of different types for antibacterial tests.

Very few cyclic hydroxamic acids have been described in the literature. 2-Hydroxyquinoline 1-oxide (" oxycarbostyril ") (III) was obtained by Friedländer and Ostermaier (*Ber.*, 1881, **14**, 1916; 1882, **15**, 332; Friedländer, *Ber.*, 1914, **47**, 3369) as a minor product of the reduction of ethyl *o*-nitrocinnamate. Heller and Wunderlich (*ibid.*, p. 2889) obtained the related oxycarbostyril carboxylic acid (IV) by reduction of *o*-nitrobenzylidenemalonic acid with zinc and acetic acid, and Reissert (*Ber.*, 1908, **41**, 3921; see also Di Carlo, *J. Amer. Chem. Soc.*, 1944, **66**, 1420) obtained 1 : 2-dioxindole (V) by reduction of *o*-nitrophenylacetic acid with zinc and sulphuric acid. Our approach to the synthesis of cyclic hydroxamic acids has been limited in the first place to attempts to oxidise *N*-heterocyclic derivatives directly to the required acid rather than the use of a final ring-closure reaction involving the simultaneous formation of the

* These experiments were made by Mr. A. H. Gowenlock, M.Sc., in the University of Manchester.

† Similar tautomeric structures can be written for the cyclic hydroxamic acids (III), (IV), (VI), (IX), and (XII).

heterocycle and the hydroxamic acid grouping, the method employed for the preparation of the hydroxamic acids mentioned above. The only other cyclic hydroxamic acid known to us,



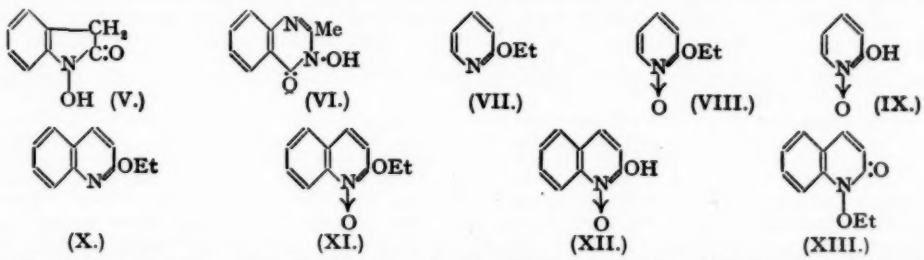
(I.) (II.) (III.) (IV.)

4-hydroxy-2-methylquinazoline 3-oxide (VI) was obtained by treatment of acetylanthranil with hydroxylamine (Anschutz, Schmidt, and Greiffenberg, *Ber.*, 1902, **35**, 3480).

In attempts to prepare a cyclic hydroxamic acid related to quinoxaline, it was found that 2-hydroxyquinoxaline is smoothly oxidised to 2 : 3-dihydroxyquinoxaline and, furthermore, that oxidation of 2-ethoxyquinoxaline gave 3-ethoxyquinoxaline 1-oxide and not 2-ethoxyquinoxaline 1-oxide (Newbold and Spring, this vol., p. 519). Similar oxidation of 2-ethoxy- and 2-chloro-pyrazine derivatives gave the corresponding 4-oxides and not the required 1-oxides (Baxter, Newbold, and Spring, this vol., p. 1859). More successful were attempts to oxidise pyridine and quinoline derivatives.

Treatment of 2-ethoxypyridine (VII) with hydrogen peroxide in acetic acid gives *2-ethoxypyridine 1-oxide* (VIII), characterised by the preparation of its *picrate*. Hydrolysis of 2-ethoxypyridine 1-oxide with dilute hydrochloric acid gives *2-hydroxypyridine 1-oxide* (IX); this has the expected properties of a cyclic hydroxamic acid, it gives a deep red colour with ferric chloride solution, it liberates carbon dioxide from sodium hydrogen carbonate solution, and it gives a crystalline *copper* salt which is soluble in dioxan. When reduced with tin and hydrochloric acid the cyclic hydroxamic acid (IX) forms 2-pyridone.

Oxidation of 2-ethoxyquinoline (X) with hydrogen peroxide gave *2-ethoxyquinoline 1-oxide hydrate* (as XI). Hydrolysis of this oxide with mineral acid gave 2-hydroxyquinoline 1-oxide (XII) (" oxycarbostyril "), identical with the product described by Friedländer and Ostermaier (*loc. cit.*). Ethylation of 2-hydroxyquinoline 1-oxide with ethyl iodide in alkaline solution gives



(V.) (VI.) (VII.) (VIII.) (IX.)

(X.) (XI.) (XII.) (XIII.)

the ethyl derivative, m. p. 71—72°, previously described by Friedländer and Ostermaier. Although this compound has the same m. p. as 2-ethoxyquinoline 1-oxide it is quite distinct from the latter and it is, probably, 2-keto-1-ethoxy-1 : 2-dihydroquinoline (XIII). Unlike 2-ethoxyquinoline 1-oxide, it is recovered unchanged after being heated with hydrochloric acid.

Antibacterial tests were made on three of the cyclic hydroxamic acids mentioned in this paper; the results are shown below :

Compound.	Minimal inhibitory concentration in mg. per 100 ml. of broth.		
	Strep. hæm.	*Staph. aureus.*	*B. coli.*
2-Hydroxypyridine 1-oxide	1	10	20
2-Hydroxyquinoline 1-oxide.....	0·1	2	1
4-Hydroxy-2-methylquinazoline 3-oxide	1	50	20

The three compounds were also tested against a bovine-type *M. tuberculosis*. With sub-surface culture in Dubos–albumin–Tween medium the first two inhibited growth at a minimum concentration of 1 : 40,000.

We are indebted to Dr. James Walker of the National Institute for Medical Research who arranged the antibacterial tests.

Experimental.

2-Ethoxyquinoline 1-Oxide.—A solution of 2-ethoxyquinoline (6·0 g.) in glacial acetic acid (50 c.c.) was treated with hydrogen peroxide (100-vol., 50 c.c.) and kept at 56° for 16 hours. The mixture was evaporated under reduced pressure, made alkaline by addition of sodium hydroxide solution, and extracted with chloroform, and the dried (Na_2SO_4) extract evaporated. The residue was dissolved in

light petroleum (b. p. 40—60°), from which the *hydrate* of 2-ethoxyquinoline 1-oxide separated as needles; after two recrystallisations from ether it had m. p. 71—73° (1·8 g.) (Found: C, 63·6; H, 6·5. $C_{11}H_{11}O_2N,H_2O$ requires C, 63·8; H, 6·3%). It is soluble in water, alcohols, chloroform, and benzene. The *picrate* separated from ethanol as yellow needles, m. p. 124—125° (Found: C, 48·8; H, 3·2; N, 13·2. $C_{17}H_{14}O_9N_4$ requires C, 48·8; H, 3·35; N, 13·4%).

2-*Hydroxyquinoline* 1-*Oxide*.—A solution of 2-ethoxyquinoline 1-oxide (0·5 g.) in ethanol (4 c.c.) and 3N-hydrochloric acid (8 c.c.) was refluxed for 2 hours. The ethanol was removed by distillation and the crystalline solid separating was collected and recrystallised from water to yield 2-hydroxyquinoline 1-oxide as plates, m. p. 189—190° not depressed when mixed with a specimen prepared as described by Friedländer and Ostermaier (*loc. cit.*). This oxide dissolves in cold sodium hydrogen carbonate solution with liberation of carbon dioxide and gives a deep red colour with ferric chloride in aqueous-alcoholic solution (Found: C, 67·1; H, 4·5. Calc. for $C_9H_7O_2N$: C, 67·1; H, 4·3%).

2-*Keto*-1-*ethoxy*-1 : 2-*dihydroquinoline*.—A solution of 2-hydroxyquinoline 1-oxide (180 mg.) in ethanol (5 c.c.) was treated with potassium hydroxide solution (7%; 1 c.c.) and ethyl iodide (0·25 c.c.) and heated under reflux for 2 hours. The alcohol was evaporated (reduced pressure), and the mixture diluted with 10% potassium hydroxide solution and extracted with ether. The ether was removed from the dried extract and the residue crystallised from light petroleum (b. p. 60—80°), from which 2-keto-1-ethoxy-1 : 2-dihydroquinoline separated as needles (160 mg.), m. p. 71—72°. A mixture with 2-ethoxyquinoline 1-oxide (m. p. 71—73°) melted between 45° and 55°. 2-Keto-1-ethoxy-1 : 2-dihydroquinoline was recovered unchanged after being heated under reflux for 12 hours with excess of 5N-hydrochloric acid (Found: C, 70·1; H, 5·9. Calc. for $C_{11}H_{11}O_2N$: C, 69·8; H, 5·8%).

2-*Ethoxypyridine* 1-*Oxide*.—2-Ethoxypyridine has been prepared by treatment of 2-pyridone in alkaline solution with ethyl iodide (Pechmann and Baltzer, *Ber.*, 1891, **24**, 3148) and by treatment of 2-aminopyridine with nitrous acid in the presence of ethanol (Tschitschibabin and Rjasanzew, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1580). The following method was found to be satisfactory: A solution of 2-bromopyridine (79 g.) in ethanolic sodium ethoxide (13·8 g. of sodium in 250 c.c. of ethanol) was refluxed for 8 hours. The product was distilled and the fraction boiling at 150—170°/755 mm. was treated with ethanolic picric acid, and the picrate recrystallised from ethanol, from which it separated as prismatic needles, m. p. 131—133° (41 g.) (Found: C, 44·7; H, 3·3. Calc. for $C_{13}H_{12}O_8N_4$: C, 44·3; H, 3·4%). The picrate was decomposed with lithium hydroxide to give 2-ethoxypyridine, b. p. 51°/11 mm. (13·5 g.; 33% allowing for recovered 2-bromopyridine).

A solution of 2-ethoxypyridine (6 g.) in glacial acetic acid (40 c.c.) was treated with hydrogen peroxide (100-vol., 40 c.c.) and kept at 56° for 20 hours. The mixture was evaporated under reduced pressure, and the residue made alkaline by addition of ice-cold 3N-potassium hydroxide. The mixture was extracted with chloroform (3 × 35 c.c.). The dried (Na_2SO_4) extract was evaporated, and the crystalline residue recrystallised from dioxan–ether to give 2-*ethoxypyridine* 1-*oxide monohydrate* as prismatic needles, m. p. 49—52°. After drying in a vacuum over phosphoric oxide for 24 hours it has m. p. 71—73°; it is extremely hygroscopic, a property which made analysis very difficult (Found: C, 58·8; H, 6·5. $C_7H_9O_2N$ requires C, 60·4; H, 6·5. $C_7H_9O_2N,H_2O$ requires C, 53·2; H, 7·0%). The *picrate* separates from ethanol as yellow needles, m. p. 111—113° (Found: C, 42·5; H, 3·4. $C_{13}H_{12}O_9N_4$ requires C, 42·4; H, 3·3%).

2-*Hydroxypyridine* 1-*Oxide*.—2-Ethoxypyridine 1-oxide (0·6 g.) was heated under reflux with hydrochloric acid (3N, 10 c.c.), and the mixture evaporated under reduced pressure. The residue was kept at 100°/10 mm. until it was solid. Sublimation at 100°/0·001 mm. gave 2-*hydroxypyridine* 1-*oxide* (350 mg.) as a crystalline mass, m. p. 149—151°; when recrystallised from dioxan–benzene it separated as blades. It is readily soluble in hot water and ethanol and insoluble in benzene, chloroform, and ether. An ethanolic solution of the hydroxamic acid gives a deep cherry-red coloration with aqueous ferric chloride solution; it dissolves readily in cold saturated sodium hydrogen carbonate solution with evolution of carbon dioxide (Found: C, 53·7; H, 4·8; N, 12·2; equiv., 114. $C_5H_5O_2N$ requires C, 54·0; H, 4·5; N, 12·6%; equiv., 111).

A concentrated aqueous solution of 2-hydroxypyridine 1-oxide was treated with a slight excess of a saturated solution of copper acetate. The *copper* salt was collected and recrystallised from dioxan, from which it separates as light blue prismatic needles, m. p. 292—294° (decomp.) [Found: C, 42·4; H, 2·8. $(C_5H_4O_2N)_2Cu$ requires C, 42·3; H, 2·8%].

A solution of the copper salt (200 mg.) in hot dioxan was diluted with water (10 c.c.) and saturated with hydrogen sulphide. The mixture was evaporated to dryness, and the residue extracted with hot ethanol. The filtered extract was evaporated to dryness, and the residue sublimed to yield 2-hydroxypyridine 1-oxide (120 mg.), m. p. and mixed m. p. 149—151°.

2-*Pyridone*.—A solution of 2-hydroxypyridine 1-oxide (300 mg.) in hydrochloric acid (*d* 1·19; 3 c.c.) was treated with granulated tin (3 g.) and heated on the water-bath for 5 hours, concentrated hydrochloric acid (1 c.c.) being added every hour. The solution was decanted, and the metal washed with distilled water. The combined solution and washings were evaporated to dryness (reduced pressure) and the solid residue suspended in warm water (30 c.c.) and treated with excess of hydrogen sulphide. The mixture was filtered, and the filtrate evaporated to dryness under reduced pressure. The residual solid was dissolved in water, the solution exactly neutralised by addition of sodium hydrogen carbonate, and again evaporated to dryness. The residue was extracted with boiling benzene, and the extract concentrated and diluted with light petroleum (b. p. 40—60°), from which 2-pyridone (100 mg.) separated as long needles, m. p. 105—107°, either alone or with a specimen prepared as described by Tschitschibabin and Rjasanzew (*J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1571). The mercuric chloride compound had m. p. 196—197° either alone or mixed with an authentic specimen (Pechmann and Baltzer, *loc. cit.*).

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374. *Short-chain Polymerisation of Styrene in Presence of Stannic Chloride and Hydrogen Chloride.*

By Gwyn Williams and (Miss) Hetty Thomas.

Hydrogen chloride inhibits the long-chain polymerisation of styrene, catalysed by stannic chloride. Styrene reacts with hydrogen chloride, in presence of stannic chloride, in carbon tetrachloride medium, to form 1-phenylethyl chloride and di-, tri-, tetra- and penta-styrenes, all of which have been isolated. The polymers are formed in increasing proportions as the initial concentration of styrene is raised. Ozonisation shows them to have the structure $CHPh{:}CH{\cdot}[CHPh{\cdot}CH_2]_n{\cdot}CHPh{\cdot}CH_3$. Distyrene does not react with hydrogen chloride and stannic chloride; but 1-phenylethyl chloride reacts (in presence of stannic chloride) with styrene and, more slowly, with distyrene to form polymers. The reactions are consistent with a mechanism in which a proton, derived from the interaction of hydrogen chloride with stannic chloride, attaches itself to the styrene molecule, forming a carbonium ion, which may form 1-phenylethyl chloride reversibly, or may grow by accretion of monomeric styrene until stabilised to form the short-chain polymers. Distyrene is accompanied by a saturated isomer, possibly an indane derivative, which may be formed by cyclisation of the carbonium ion.

In carbon tetrachloride solution, in presence of stannic chloride, styrene polymerises to form polymers of molecular weight 1500—3000 (cf., *e.g.*, Williams, *J.*, 1940, 775). Traces of hydrogen chloride can inhibit polymerisation temporarily but completely (Williams, *Nature*, 1937, **140**, 363), hydrogen chloride being consumed while acting as inhibitor. When a continuous supply of hydrogen chloride is led into a carbon tetrachloride solution of styrene and stannic chloride, there is no long-chain polymerisation; instead, 1-phenylethyl chloride, distyrene, and "short-chain polystyrene" are formed, in proportions which depend upon the initial concentration of styrene (Williams, *J.*, 1938, 1046). To support a kinetic study (now in progress), we have re-examined the products of this reaction; and new experiments, described in this paper, have proved the "short-chain polystyrene" to be mainly tristyrene and tetrastyrene, with some pentastyrene. Experiments covering a range of initial styrene concentrations have determined the extent to which the proportions of the reaction products may vary. In these experiments, shown in Tables I and II, dry hydrogen choride was led into solutions of styrene and stannic chloride in carbon tetrachloride at 20—25°, until the whole of the styrene had been consumed, as indicated by titration of the residual styrene with bromine (Williams, *J.*, 1938, 246). (In some experiments, at the higher styrene concentrations, the reactions were continued for times—enclosed in parentheses in the tables—which were much longer than those required for complete consumption of the original styrene.)

At the lowest styrene concentrations, a maximum of 75% of styrene is recovered as 1-phenylethyl chloride, whose structure follows from its conversion into 2 : 3-diphenylbutane. This is the normal product of addition of hydrogen chloride to the styrene double bond (Schramm, *Ber.*, 1893, **26**, 1709; cf. Walling, Kharasch, and Mayo, *J. Amer. Chem. Soc.*, 1939, **61**, 2693, for the analogous hydrogen bromide addition).

The proportion of 1-phenylethyl chloride in the product falls with rising initial concentration of styrene; and the yield of distyrene appears to reach a maximum of 40% at about 2·5M-styrene (Expts. 13, 20, 24). The yields of the products called in Table I "short-chain polystyrene" increase at still higher styrene concentrations (*e.g.*, in Expts. 37 and 38). The short-chain polystyrene consists mainly of tri-, tetra-, and penta-styrenes, all of which can be distilled at pressures of 1 mm.; but it also contains a certain proportion of polymer, with higher molecular weight, which does not distil under the conditions employed. Expt. 38, carried out with 30 g. of styrene at 5·3M-concentration, shows that the amount of non-distillable polymer formed does not exceed 8% of the initial styrene; and it may be supposed that non-distillable polymer is formed in smaller proportions at lower styrene concentrations. However, in experiments performed with smaller initial amounts of styrene, the attempted quantitative separation of distillable from non-distillable polymer tends to exaggerate the latter (*e.g.*, in Expt. 37). Only at the highest styrene concentrations employed does the non-distillable polymer residue contain polystyrene of high enough molecular weight to be capable of precipitation in methyl alcohol. The mean (cryoscopic) molecular weight of a non-distillable residue from 4M-initial styrene was 633. The non-distillable residue from 5·3M-styrene contained 3·8% of the initial styrene as polymer, with mean molecular weight 881, which was precipitated by methyl alcohol. These molecular weights are much smaller than those (up to 3,000) obtained at comparable styrene concentrations in the absence of hydrogen chloride.

It should be noted that, in experiments of long duration (*e.g.*, cf. Expts. 24 and 20 of Table II),

the yields of individual products may have been affected by interaction between 1-phenylethyl chloride and distyrene (cf. Table III) after the initial styrene had been used up.

TABLE I.

Interaction of styrene with hydrogen chloride and stannic chloride. Solvent: Carbon tetrachloride. Temp.: 20—25°. *Dry hydrogen chloride led through solutions.* (*Concn. of* HCl: 0·14M.)

				% Styrene recovered as:			
Expt. no.	Styrene concn., M.	$SnCl_4$ concn., M.	Time, mins.	C_8H_9Cl.	$C_{16}H_{16}$.	Short-chain polystyrene.	Total yield, %.
10	0·08	0·044	180	73·9	←------ 11 ------→		84·9
11	0·08	0·044	187	74·0	←------ 20·1 ------→		94·1
9	0·17	0·026	172	75·0	15·0	3·9	93·9
6	0·17	0·035	210	64·0	7·3	9·9	81·2
7	0·17	0·044	186	69·0	7·1	5·5	81·6
1	1·11	0·022	183	58·0	7·9	14·0	79·9
4	1·73	0·044	(150)	38·0	←------ 54·0 ------→		92·0
14	1·73	0·088	(182)	50·5	31·7	16·1	98·3
13	2·5	0·088	(180)	22·1	40·2	33·9	96·2
5	3·4	0·088	(175)	8·5	12·0	66·0	86·5
12	3·4	0·088	(180)	2·4	29·1	57·2	88·7
37	4·0	0·088	10	11·1	31·3	54·5 *	96·9
38	5·3	0·088	12	7·4	27·4	59·2 †	94·0
3	5·3	0·088	(180)	2·0	9·0	59·0 ‡	70·0
31 §	1·73	0·044	(90)	21·1	37·4	23·0	81·5
30 §	2·5	0·088	(105)	6·2	9·0	50·4	65·6

* Containing at least 23·5% of the initial styrene as tri- and tetra-styrenes.
† Short-chain polystyrene composed of 24·0% of initial styrene as fraction with b. p. 185—300°/12 mm. (mainly tristyrene); 27·3% as fraction with b. p. 300—360°/12 mm. (mainly tetra- and penta-styrenes); and 7·9% as distillation residue.
‡ 3·8% of styrene recovered as polymer insoluble in methyl alcohol.
§ At 76°.

Structures of the Polymers.—The distyrene has already been identified (*J.*, 1938, 1046) as the one prepared by Erlenmeyer (*Annalen*, 1865, **135**, 122), by Fittig and Erdmann (*ibid.*, 1883, **216**, 179), by Stoermer and Kootz (*Ber.*, 1928, **61**, 2330), and by Risi and Gauvin (*Canadian J. Res.*, 1936, *B*, **14**, 255). Stobbe and Posnjak (*Annalen*, 1909, **371**, 287) proved it to be 1 : 3-diphenylbut-1-ene (I) (see p. 1870). The identification of the distyrene of Table I with this compound is still further strengthened in the experimental section. When isolated as a product of the reaction of styrene with hydrogen chloride and stannic chloride, this distyrene is, however, accompanied by a saturated isomer (see next paragraph).

The tristyrene and tetrastyrene isolated from experiments with high initial styrene concentrations both give benzaldehyde on ozonisation. It therefore seems probable that they are, respectively, 1 : 3 : 5-triphenylhex-1-ene (III) and 1 : 3 : 5 : 7-tetraphenyloct-1-ene (IV). It may be recalled that Stoermer and Kootz (*loc. cit.*) obtained benzaldehyde and hydratropic aldehyde by ozonisation of distyrene of structure (I), whereas Staudinger and Steinhofer (*Annalen*, 1935, **517**, 35) obtained no analogous products by oxidation of the differently constituted di- and tri-styrenes isolated from the products of pyrolysis of long-chain polystyrene.

Some pentastyrene was isolated by distillation of the combined polymer products of several experiments. There is no reason against supposing that its structure is analogous to those of the smaller polymers.

Saturated Distyrene.—When isolated from the reaction mixture, the distyrene is usually found to be heavily contaminated with a saturated isomer. Table II shows the extent of unsaturation of the distyrene in a number of experiments, as determined by addition of iodine chloride or bromine to the double bond. Formation of distyrene dibromide from the partially saturated material, followed by regeneration of the olefin by the action of zinc, gave distyrene 99·5—100% unsaturated, as estimated by the same procedure, always supposing the molecule to contain one double bond.

The formation of the saturated distyrene is not surprising, because stannic chloride is known to catalyse the conversion of the unsaturated distyrene (I) into a saturated isomer (Risi and Gauvin, *loc. cit.*). The structure of the saturated dimer has not been proved. By analogy with the known structures of the saturated dimers of 1-methylstyrene and 1 : 1-diphenylethylene (Schoepfle and Ryan, *J. Amer. Chem. Soc.*, 1930, **52**, 4021; Bergmann and Weiss, *Annalen*, 1930, **480**, 49; Bergmann, Taubadel, and Weiss, *Ber.*, 1931, **64**, 1493) the saturated

TABLE II.

Extent of unsaturation of distyrene.

Expt. no.	Initial styrene, M.	$SnCl_4$, M.	Time, mins.	% Styrene recovered as: C_8H_9Cl.	$C_{16}H_{16}$.	% Unsaturation of $C_{16}H_{16}$.
28	1·73	0·085	28	31	30	27·7
25	1·89	0·048	45	45·1	12	47
27	1·89	0·048	33	30·5	26·4	38
29	2·02	0·021	71	29·2	19·1	36
26	2·31	0·044	46	39·5	28	31
23	2·5	0·04	25	24	31	20
24	2·5	0·04	15	33	37	20
20	2·5	0·04	(120)	13	37	76
22	2·5	0·04	(120)	14	36	23

distyrene has been supposed (Risi and Gauvin, *loc. cit.*; Stanley, *Chem. and Ind.*, 1939, **58**, 1080) to be 1-phenyl-3-methylindane (II), contrary to the opinion of Stoermer and Kootz (*loc. cit.*), who thought that the isomer was unsaturated.

In the absence of a catalyst, the isomerisation of distyrene is not at all rapid; distyrene from a reaction product, initially 96% unsaturated, was still 94% unsaturated when retested after standing in daylight for 19 days.. The conversion of distyrene, initially 100% unsaturated, into the saturated isomer in presence of stannic chloride is shown in Expts. 35 and 36 of Table III.

A specimen of tristyrene, isolated from the reaction products, gave a halogen absorption (in 75 mins.) corresponding to 68·5% unsaturation; but halogen absorption is slow and is not a very certain method for the quantitative estimation of unsaturation in polystyrenes (cf. Staudinger and Steinhofer, *loc. cit.*). On the other hand, the formation of 1-phenyl-3-(2′-phenyl-*n*-propyl)indane from tristyrene (III) is not impossible; and Risi and Gauvin (*loc. cit.*) have suggested that this kind of cyclisation may be a possible chain-termination process in the long-chain polymerisation of styrene.

Mechanism of the Reaction.—The products listed in Tables I and II can react further among themselves. This is shown by the results given in Table III. Experiments described in an earlier paper (*J.*, 1938, 1046) have already proved:

(1) that styrene and hydrogen chloride do not react together in the absence of a catalyst;

(2) that racemic 1-phenylethyl chloride does not undergo any substantial change under the influence of stannic chloride, 90% of the original material being recovered unchanged after contact for 140 mins. in carbon tetrachloride medium.

The results of Table III show:

(3) that distyrene does not change appreciably under the combined action of hydrogen chloride and stannic chloride, except for a slow conversion to its saturated isomer (Expts. 15, 35, 36);

(4) but that 1-phenylethyl chloride reacts with styrene (Expts. 32, VIII) and, more slowly, with distyrene (Expt. 33) to form polymers. This is particularly evident from the

TABLE III.

Further interactions of products.

Current of hydrogen chloride passed only in Expts. 15, 35, 36.

Expt. no.	Starting materials.	$SnCl_4$ concn., M.	Time, mins.	% Styrene recovered as: C_8H_9Cl.	$C_{16}H_{16}$.	$(C_8H_8)_{3-4}$.	Non-dist. polymer.	Total yield.
15	$C_{16}H_{16}$* : 0·89M	0·088	180	0	92·2	0	4	96·2
35	$C_{16}H_{16}$† : 0·53M	0·047	75	0	91·0‖			91·0
36	$C_{16}H_{16}$‡ : 2·06M	0·047	75	0	90·0¶			90·0
32§	C_8H_8 : 1·81M (0·079) C_8H_9Cl : 0·92M (0·040)	0·080	92	2·1 (0·0026)	41·6 (0·050)	30·7 (0·037)	17·3 (0·024)	91·7
VIII§	C_8H_8 : 1·7M (0·14) C_8H_9Cl : 0·75M (0·060)	0·086	1500	0 ← 66 →	20 (0·050)	(0·16)		86
33§	$C_{16}H_{16}$† : 0·87M (0·073) C_8H_9Cl : 0·75M (0·030)	0·080	385	16·4 (0·017)	53·0 (0·055)	19·8 (0·020)	2·5 (0·0026)	91·7

* Partly saturated. ‖ 95% unsaturated.
† 100% unsaturated. ¶ 87% unsaturated
‡ 95·5% unsaturated.

§ Moles of starting materials corrected for amounts of solution extracted for analysis. Yields calculated on total C_8H_8 in combined C_8H_8 and C_8H_9Cl. Moles of polystyrene always given as moles of C_8H_8 in given weight of polymer. Experiment VIII taken from *J.*, 1938, 1046.

numbers of moles of starting materials and end products, given in parentheses for the relevant experiments in Table III. In the long experiment VIII, the 1-phenylethyl chloride is completely consumed.

The following suggested interpretation of the reactions is based upon the evidence which exists that an alkyl halide and a metal halide catalyst form a complex which is ionised, though not necessarily much *dissociated* into free ions in a solvent of low dielectric constant (cf., *e.g.*, Fairbrother, *Trans. Faraday Soc.*, **1941**, **37**, 763; Price, *Chem. Reviews*, 1941, **29**, 37). The free ions represented in the equations would perhaps be more properly visualised as ion pairs, themselves existing, in a carbon tetrachloride medium, in small concentration only (Fairbrother, *J.*, 1945, 503).

" Normal " polymerisation :

$$CHPh{:}CH_2 + SnCl_4 \rightleftharpoons \overset{+}{C}HPh\cdot CH_2\cdot\overline{Sn}Cl_4 \quad (1)$$

$$CHPh{:}CH_2 + \overset{+}{C}HPh\cdot CH_2\cdot\overline{Sn}Cl_4 = \overset{+}{C}HPh\cdot CH_2\cdot CHPh\cdot CH_2\cdot\overline{Sn}Cl_4, \text{ etc.} \quad (2)$$

In presence of hydrogen chloride :

$$HCl + SnCl_4 \rightleftharpoons H^+ + SnCl_5^- \quad (3)$$

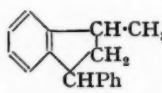
$$CHPh{:}CH_2 + H^+ = \overset{+}{C}HPh\cdot CH_3 \quad (4)$$

$$\overset{+}{C}HPh\cdot CH_2\cdot\overline{Sn}Cl_4 + H^+ = \overset{+}{C}HPh\cdot CH_3 + SnCl_4 \quad (5)$$

$$\overset{+}{C}HPh\cdot CH_3 + HCl = CHPhCl\cdot CH_3 + H^+ \quad (6)$$

$$\overset{+}{C}HPh\cdot CH_3 + SnCl_5^- \rightleftharpoons CHPhCl\cdot CH_3 + SnCl_4 \quad (7)$$

$$\overset{+}{C}HPh\cdot CH_2\cdot\underbrace{CHPh\cdot CH_3}_{\text{(I.)}} + SnCl_5^- = CHPh{:}CH\cdot CHPh\cdot CH_3 + HCl + SnCl_4 \quad (8)$$

(8) $\xrightarrow{CHPh:CH_2}$ (I.) $\dashrightarrow$  + HCl + $SnCl_4$ (9)

(II.)

$$\overset{+}{C}HPh\cdot[CH_2\cdot CHPh]_2\cdot CH_3 + SnCl_5^- = \underbrace{CHPh{:}CH\cdot CHPh\cdot CH_2\cdot CHPh\cdot CH_3}_{\text{(III.)}} + HCl + SnCl_4 \quad (10)$$

(III.) $\xrightarrow{CHPh:CH_2}$

$$\overset{+}{C}HPh\cdot[CH_2\cdot CHPh]_3\cdot CH_3 + SnCl_5^- = \underbrace{CHPh{:}CH\cdot[CHPh\cdot CH_2]_2\cdot CHPh\cdot CH_3}_{\text{(IV.)}} + HCl + SnCl_4 \quad (11)$$

In the absence of hydrogen chloride, stannic chloride catalyses the polymerisation of styrene to relatively long-chain products, *e.g.*, with 1·7M-initial styrene, to molecules of the order $(C_8H_8)_{23}$.

If catalysts of the " Friedel–Crafts " type initiate polymerisation by polarising the olefinic double bond (cf., *e.g.*, Price, *Ann. New York Acad. Sci.*, 1943, **44**, 351; Hulburt, Harman, Tobolsky, and Eyring, *ibid.*, p. 371), the " normal " polymerisation may be propagated by processes of the type shown in equations (1) and (2). The presence of hydrogen chloride prevents the " normal " polymerisation: with 1·7M-styrene in presence of stannic chloride and 0·14M-hydrogen chloride, none of the material formed can be precipitated in methyl alcohol, and the largest polymer isolated is $(C_8H_8)_{3-4}$, in about 16% yield (Table I, expt. 14). The reaction in presence of hydrogen chloride is also faster than the " normal " polymerisation in its absence. This is shown in Table IV, which contains results taken from previous work on the " normal " polymerisation (cf. *J.*, 1940, 775), together with figures from Tables I and II, above.

TABLE IV.

Stannic chloride: 0·04—0·05M

Concn. C_8H_8, M	0·17	0·35	0·86	1·7	1·9	2·5	3·5	4·0
" Normal " polymerisation in absence of hydrogen chloride.								
% Consumption of C_8H_8	—	46	50	61	—	—	84	—
Time, mins.	—	5400	1600	190	—	—	162	—
Reaction with 0·14M-HCl; complete consumption of styrene in:								
Time, mins.	186	—	—	—	33	15	—	10

It follows that the formation of the products shown in Tables I and II cannot be due to the interruption of " normal " polymerisation chains, since the latter are initiated too slowly to account for the formation of these products within the times observed. Hydrogen chloride and stannic chloride in combination must act in two ways : (*a*) in stopping the " normal " polymerisation chains, and (*b*) in propagating much shorter chains by a different mechanism. The polymerisation complex of equation (1) must either be decomposed into styrene by hydrogen chloride; or it must be diverted by hydrogen chloride into an alternative path (equation 5).

The combined catalytic action of hydrogen chloride and stannic chloride in carbon tetrachloride resembles the catalytic action of aqueous sulphuric or hydrochloric acid upon styrene (Risi and Gauvin, *loc. cit.*) in producing small polymers only. In the presence of stannic chloride, therefore, the catalytic behaviour of hydrogen chloride is similar to that of a strong acid. By analogy with the influence exerted by Friedel–Crafts catalysts upon alkyl halides, it seems probable that hydrogen chloride and stannic chloride will react, in carbon tetrachloride, as shown in equation (3). (Alternatively, $SnCl_6^{--}$ may be formed.) Evidence for some such interaction may be seen in Meerwein's observation (*Annalen*, 1927, **453**, 16) that dilute ethereal solutions of hydrogen chloride and of stannic chloride are, separately, *yellow* after addition of the indicator *p*-dimethylaminoazobenzene; but that an immediate *red* colour is formed as soon as the two yellow solutions are mixed. The virtually free proton from (3) may react with styrene, as in (4), or may decompose the " normal " polymerisation complex, as in (5), forming, in either event, a carbonium ion, which can be converted into 1-phenylethyl chloride by (7), and perhaps also by (6). The reaction (7) must be supposed reversible to account for Bodendorf and Böhme's discovery (*Annalen*, 1935, **516**, 1) that optically active 1-phenylethyl chloride is racemised by the action of stannic chloride (interpreted by these authors by equations equivalent to 7); and also to account for the reactions of 1-phenylethyl chloride with styrene and distyrene (Table III). (Cf., also, the elimination equilibrium discussed by Hughes, Ingold, and Scott, *J.*, 1937, 1271.) The formation of the polystyrenes (I), (III), and (IV) is represented by the addition of monomeric styrene to a carbonium ion of increasing chain length, coupled with the stabilisation processes, typified by (8), which are evidently more efficient than the chain-termination processes occurring in the normal polymerisation in absence of hydrogen chloride. The stabilisation reactions are not reversible; because distyrene does not polymerise further in the presence of hydrogen chloride and stannic chloride (Table III), though it does undergo slow isomerisation into its saturated isomer (II). In view of the slowness of this isomerisation (Table III, expts. 35, 36), it seems doubtful whether the substantial amounts of saturated distyrene in the reaction products can be formed by direct isomerisation within the times observed (Table II, expts. 23—29). It is more probable that the saturated distyrene (II) is produced by cyclisation of the carbonium ion, through attack by the positive end of the ion upon the benzene ring, with elimination of a proton (equation 9).

Whether styrene *must* be in the form of a complex with the catalyst in order to take up a proton, as in (5), cannot be certain; but equation (4) seems to represent a likely reaction. The general question, whether the hydrocarbon component in a Friedel–Crafts alkylation needs to be activated by association with the catalyst, has been raised by Ingold (*Trans. Faraday Soc.*, 1941, **37**, 769).

Experimental.

Materials.—Pure commercial styrene, stabilised with quinol, was redistilled before use. The stannic chloride was obtained from early fractions taken off during the distillation (in a vacuum) of stannic chloride prepared from tin and chlorine. The reaction medium was AnalaR carbon tetrachloride, dried before use. Distyrene (I) was made in quantity (cf. Risi and Gauvin, *loc. cit.*) by refluxing styrene (90 g.) for 8 hours with concentrated sulphuric acid (59 g.) and water (48 g.). The preparations gave 82% yields of distyrene, 67—79% unsaturated, from which the dibromide was prepared (in acetic acid). The action of zinc upon the dibromide gave up to 76% yield of distyrene, 99·5—100% unsaturated.

The reactions referred to in Tables I and II were carried out by leading a stream of dry hydrogen chloride through solutions of styrene (10—30 g.) and stannic chloride in carbon tetrachloride at 20—25°. When all the styrene had been consumed, the reaction products were isolated as described previously (1938), by washing the reaction mixture with water, drying and separating into fractions by distillation under reduced pressure.

Identification of Reaction Products.—The following products were isolated. (Molecular weights were determined cryoscopically in benzene solution. Analyses are by Drs. Weiler and Strauss, Oxford.)

(1) 1-Phenylethyl chloride, b. p. 81—82°/18 mm. (Found : C, 68·2; H, 6·4; Cl, 25·3. Calc. for C_8H_9Cl : C, 68·3; H, 6·4; Cl, 25·3%). The position of the chlorine atom in the molecule follows (*a*) from the ease with which it is eliminated by shaking with aqueous silver nitrate, (*b*) from the conversion of the compound into 2 : 3-diphenylbutane. 1-Phenylethyl chloride (7 g.) and sodium (2·5 g.) were left in dry ether (50 c.c.) for 5 days at 20°. The products isolated were : crystalline 2 : 3-diphenylbutane,

m. p. 123—124° (Found : C, 91·4; H, 8·6. Calc. for $C_{16}H_{18}$: C, 91·4; H, 8·6%), its liquid stereoisomer (Found : C, 91·8; H, 8·6%), and traces of unchanged halide and resin. These results are exactly as described by Ott (*Ber.*, 1928, **61**, 2142) for the action of sodium upon 1-phenylethyl chloride.

(2) Distyrene, b. p. 173—174°/16 mm., 135—137°/<1 mm. (Found : C, 92·1; H, 7·8; *M*, 207. Calc. for $C_{16}H_{16}$: C, 92·3; H, 7·7%; *M*, 208). The distyrene generally contained a detectable trace of halogen, difficult to remove by distillation or by washing with water or silver nitrate solution. On oxidation with chromium trioxide in acetic acid, the distyrene gave benzoic acid, which is consistent with the structure (I). After recrystallisation from alcohol, the dibromide of the distyrene had m. p. 101—102·5°; but this material was separated, by further recrystallisations from ether–petroleum ether mixture, into fractions having m. p. 129—130° (Found : Br, 43·1. Calc. for $C_{16}H_{16}Br_2$: Br, 43·4%) and 119—120°; a very small amount of a further fraction, with m. p. 70—72°, was obtained from the mother-liquor. These results for the dibromide correspond closely to those found by Stoermer and Kootz (*loc. cit.*) for the dibromide of distyrene having the structure (I), the substance of m. p. 102° being a mixed crystal, separable into stereoisomers.

The extent of unsaturation of distyrene (cf. Tables II and III) was measured by running 5 c.c. of a carbon tetrachloride solution of distyrene into excess of standard iodine chloride (or bromine) solution in acetic acid, followed by titration of the residual halogenating agent (after varying times of exposure of the distyrene to the halogen, in order to ensure complete addition). Some specimen results are shown in Table V.

TABLE V.

Concn. $C_{16}H_{16}$, M	0·0609	0·0928	0·0923	0·0902
Concn. unsat. $C_{16}H_{16}$ found, M : after 5 mins.	0·0609	0·0886	0·0803	0·0253
after 10 mins.	0·0610	0·0887	0·0801	0·0251
% of unsat. isomer in $C_{16}H_{16}$	100	95·6	87·0	27·9

(3) Tristyrene, a faintly yellow, viscous oil, showing a pale-blue fluorescence, b. p. 214—215°/<1 mm. (Found for different preparations : C, 91·9, 92·1, 92·0, 91·7; H, 7·9, 7·6, 8·0, 8·0; *M*, 324, 312, 308, 311. Calc. for $C_{24}H_{24}$: C, 92·3; H, 7·7%; *M*, 312). Attempts to prepare a dibromide gave only a semi-solid mass, which is not surprising in view of the number of possible stereoisomers.

(4) Tetrastyrene, a very viscous oil. A sample prepared from 4M-styrene and 0·04M-stannic chloride had b. p. 255—258°/<1 mm. (Found : C, 92·2; H, 7·8; *M*, 412. Calc. for $C_{32}H_{32}$: C, 92·3; H, 7·7%; *M*, 416).

(5) Pentastyrene, b. p. 280—300°/<1 mm., *M*, 513 (calc. : 520), was isolated by distillation of the combined polymers from several reaction mixtures. It was exceedingly viscous.

Ozonisation Experiments.—The tri- and tetra-styrenes were ozonised in acetic acid solution. After decomposition of the ozonides with zinc and water, the resulting aldehydes were converted into their 2 : 4-dinitrophenylhydrazones. Benzaldehyde proved to be a principal product from both ozonisations, as would be expected from the structures (III) and (IV). The benzaldehyde 2 : 4-dinitrophenylhydrazone, separated by chromatography on a column of alumina, had the following characteristics : (*a*) from tristyrene (Found : C, 54·8; H, 3·8. Calc. for $C_{13}H_{10}O_4N_4$: C, 54·5; H, 3·5%), m. p. 236—237°; mixed m. p. with authentic specimen, 233—234°; (*b*) from tetrastyrene (Found : C, 54·6; H, 3·8%), m. p. 234—235°; mixed m. p. with authentic specimen, 233·5—234·5°; m. p. of authentic specimen, 234—235°.

We thank the Chemical Society for a grant from the Research Fund, the Distillers Company Limited and Messrs. Peter Spence and Sons, Ltd., for gifts of materials, and Dr. E. R. H. Jones and Professor Sir Ian Heilbron, F.R.S., for allowing us facilities for carrying out the ozonisations.

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375. *Some Trinuclear Cyanine Dyes. Part II. Neocyanines with Dissimilar Nuclei.*

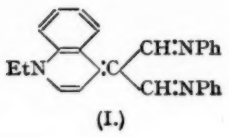
By FRANCES M. HAMER, RUSSELL J. RATHBONE, and BARBARA S. WINTON.

N-Alkyldihydro-derivatives of heterocyclic bases, with a dianil*iso*propylidene group in the reactive position, were condensed with two mols. of heterocyclic quaternary ammonium salts, having a reactive methyl group, to give *neocyanines* with two similar nuclei and one dissimilar, the two similar nuclei being at the ends of the pentamethin chain. The dianils were also condensed with one mol. of quaternary salts, to give intermediate *dyes* having two nuclei and one anilomethyl group; these gave rise to *isomerides* of the above neocyanines, having the two similar nuclei at the ends of a trimethin chain, and also to *neocyanines* with three dissimilar nuclei. Absorption maxima of methyl-alcoholic solutions of the new dyes were compared with those of such related simpler dyes as have chain-systems which build up the complex chains of the neocyanines and intermediates.

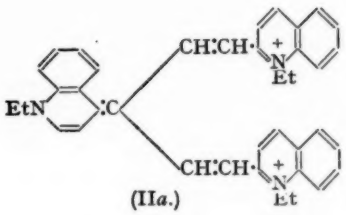
NEOCYANINE was the name given to a by-product obtained in the preparation of 4 : 4′-trimethincyanine. Its trinuclear nature had been known for nineteen years (Hamer, *J.*, 1928, 1472) and its possible constitution for twelve (König, *Z. wiss. Phot.*, 1935, **34**, 15), before our

synthesis of it from the dianilo-base (I) established that it has two 4-linked quinoline nuclei connected by an unbranched pentamethin chain, with a third such nucleus attached in the *meso*-position (Hamer, Rathbone, and Winton, *J.*, 1947, 1434). We also synthesised other neocyanines containing three similar heterocyclic nuclei; two of these were identical with dyes which had previously been obtained empirically, whilst five were new. For this work nine dianilo-compounds besides (I) were themselves synthesised.

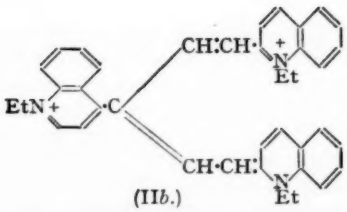
The present paper shows the synthetic method to have enormously greater scope than the empirical one. Thus one molecule of a dianilo-compound such as (I) may be condensed with two molecules of any quaternary, heterocyclic ammonium salt, having a reactive methyl group, and if the nucleus of the salt differs from that of the dianilo-compound, neocyanines having two similar nuclei and one dissimilar will result. For instance, by condensing (I) with quinaldine ethiodide, we prepared a *dye* of which the kation may be represented by the three resonating



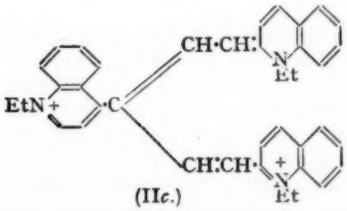
(I.)



(II*a*.)

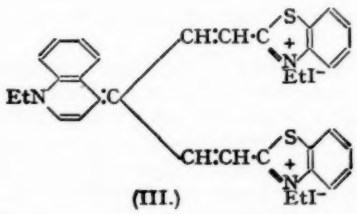


(II*b*.)

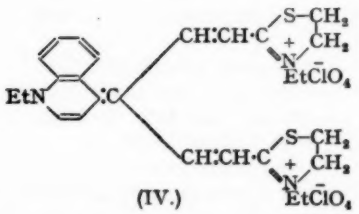


(II*c*.)

structures (II*a*), (II*b*), and (II*c*). The use of 2-methylbenzthiazole ethiodide or 2-methyl-Δ^2-thiazoline ethiodide instead of quinaldine ethiodide led to the *neocyanines* represented, respectively, by formulæ (III) and (IV), to give for each substance only one out of each group of three canonical structures. An *isomeride* of (III), having a 1 : 2- instead of a 1 : 4-dihydroquinoline nucleus, was prepared by condensing the 1 : 2-isomeride of (I) with 2-methylbenzthiazole ethiodide. By condensing a dianilo-compound having a benzthiazoline nucleus with lepidine ethiodide we prepared (V); with quinaldine ethiodide this dianil gave an *analogue* of



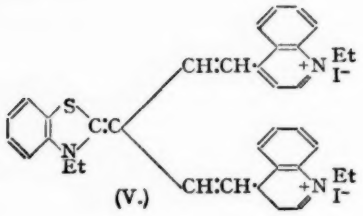
(III.)



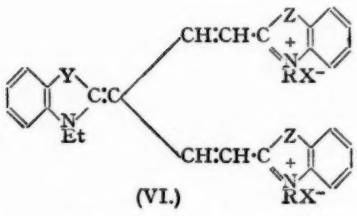
(IV.)

(II), in which a benzthiazole nucleus took the place of the 4-linked quinoline; with 2-methylbenzoxazole ethiodide and 2-methylbenzselenazole ethiodide, respectively, it gave *dyes* represented by (VI; Y = S, R = Et, X = I, Z = O or Se). By condensing a dianil having a 6 : 7-benzbenzthiazoline nucleus with 2-methyl-6 : 7-benzbenzoxazole ethiodide we obtained (VII). From a dianil having a benzselenazoline nucleus and quinaldine etho-*p*-toluenesulphonate we prepared an *analogue* of (II), with a benzselenazole in place of the 4-linked quinoline nucleus; this dianil on reacting with 2-methylbenzoxazole ethiodide and 2-methylbenzthiazole ethiodide, respectively, gave (VI; Y = Se, R = Et, X = I, Z = O or S); it was also condensed with 2-methyl-6 : 7-benzbenzthiazole etho-*p*-toluenesulphonate and with 1 : 3 : 3-trimethylindolenine methiodide, the latter yielding (VI; Y = Se, R = Me, X = ClO_4, Z = CMe_2), accompanied by an unsymmetrical *trimethincyanine* as by-product. Further *neocyanines* were prepared by condensing a dianil having a 4-methyl-Δ^4-thiazoline nucleus with

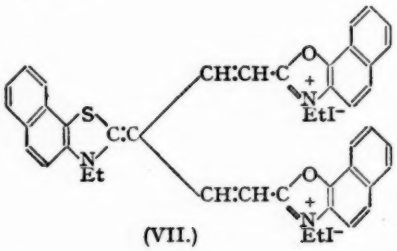
2-methylbenzthiazole ethiodide and with 2-methylbenzselenazole ethiodide, and by condensing a dianil having a thiazolidine nucleus with lepidine ethiodide and with 2-methylbenzthiazole ethiodide.



(V.)



(VI.)



(VII.)

The absorption curves of methyl-alcoholic solutions of the neocyanines were plotted and their maxima are recorded in Table I. Like neocyanines having three similar nuclei, these also had narrow, well-defined curves, with sometimes an inflexion on the side of shorter wave-length. We have here, as also in the first paper of the series, compared each absorption maximum with those of the corresponding tri- and penta-methincyanines. Whereas in Part I both parent dyes were symmetrical, here only the pentamethincyanine is symmetrical whilst the trimethincyanine is unsymmetrical. The abbreviations used in the table are obvious if taken in conjunction with the text. To each maximum that has been previously recorded, a bibliographic reference is given, and all those with no reference belong to compounds described here. Six of the parent *trimethincyanines* were prepared for the purpose of this comparison. With nineteen of the twenty neocyanines, as for the seven already described (Hamer, Rathbone, and Winton, *loc. cit.*), the absorption maximum lay between those of the corresponding unsubstituted tri- and penta-methincyanines. For these nineteen the bathochromic shifts on passing from trimethincyanine to neocyanine varied from 20 to 1675 A., whilst the anomalous hypsochromic shift on passing from the trimethincyanine to the neocyanine (IV) was 495 A. In all nineteen instances, there was a bathochromic shift on passing from neocyanine to pentamethincyanine, the amounts varying from 180 to 900 A. Many other comparisons may also be made from this table.

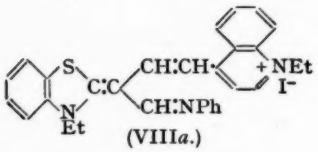
For preparing neocyanines with three similar nuclei (*idem, ibid.*) or the above neocyanines with two similar nuclei and one dissimilar, our usual procedure was to heat a mixture of dianil and quaternary salt with pyridine, which often gave a result as good as did the alternative of heating with sodium acetate in acetic anhydride. In instances where it gave an unsatisfactory product, we resorted to the latter method, which proved more drastic. When a dianil, such as that having a benzthiazoline nucleus, was mixed with a quaternary salt, *e.g.*, lepidine ethiodide, a purple colour appeared directly the pyridine was added, although heat was necessary to develop the bluer colour of the neocyanine (V). These observations led to the discovery that such reactions can be stopped when one molecule of dianil has reacted with only one molecule of quaternary salt. With the reactants specified, the resultant product is a *dye*, which may be represented by two canonical resonating structures (VIII*a*) and (VIII*b*). In the presence of acid there are three ways in which two positive charges can be distributed between the three basic groups and these may be represented by formulæ (IX*a*), (IX*b*), and (IX*c*). By causing 3-ethyl-2-dianil*iso*propylidenebenzthiazoline to react with other quaternary salts we prepared *dyes* analogous to (VIII) but having the 4-linked quinoline nucleus replaced by a 2-linked quinoline, a benzthiazole, a benzselenazole, a substituted indolenine, and a Δ^2-thiazoline nucleus, respectively. Other such *dyes* were prepared by reaction of a dianil having a 4-methyl-Δ^4-thiazoline nucleus with lepidine ethiodide, quinaldine ethiodide and 2-methyl-Δ^2-thiazoline ethiodide, and by reaction of a dianil having a thiazolidine nucleus with the alkiodide of lepidine

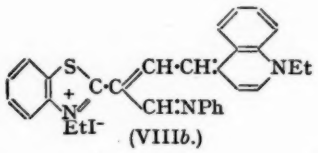
TABLE I.

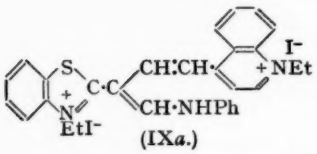
Neocyanine.	Abs. max. (A.)	Trimethincyanine.	Abs. max. (A.)	Pentamethincyanine.	Abs. max. (A.)	Bathochromic shifts. Trimethin- to neocyanine.	Bathochromic shifts. Neo- to pentamethincyanine.
4-q, 2-q, 2-q (II)	6725	4-q, 2-q	6560 †	2-q, 2-q	7080 *	165	355
4-q, bzth, bzth (III)	6320	4-q, bzth	6300 †	bzth, bzth	6500 *	20	180
4-q, thiazoline, thiazoline (IV)	5270	4-q, thiazoline	5765	thiazoline, thiazoline	5450 ‡	−495	180
2-q, bzth, bzth	6180	2-q, bzth	5600 †	bzth, bzth	6500 *	580	320
bzth, 4-q, 4-q (V)	7200	bzth, 4-q	6300 †	4-q, 4-q	8100 *	900	900
bzth, 2-q, 2-q	6365	bzth, 2-q	5600 †	2-q, 2-q	7080 *	765	715
bzth, thiazoline, thiazoline	5045	bzth, thiazoline	5020	thiazoline, thiazoline	5450 ‡	25	405
bzth, bzox (VI; Y = S, Z = O, R = Et, X = I)	5400	bzth, bzox	5200 †	bzox, bzox	5800 *	200	400
bzbzth, bzbzox	5700	bzbzth, bzbzox	5500 †	bzbzox, bzbzox	6080 *	200	380
bzth, bzSe (VI; Y = S, Z = Se, R = Et, X = I)	6155	bzth, bzSe	5620 †	bzSe, bzSe	6600 *	535	445
bzSe, 2-q, 2-q	6435	bzSe, 2-q	5820 †	2-q, 2-q	7080 *	615	645
bzSe, bzox (VI; Y = Se, Z = O, R = Et, X = I)	5465	bzSe, bzox	5270 †	bzox, bzox	5800 *	195	335
bzSe, bzth (VI; Y = Se, Z = S, R = Et, X = I)	6085	bzSe, bzth	5620 †	bzth, bzth	6500 *	465	415
bzSe, bzbzth	6405	bzSe, bzbzth	5810 †	bzbzth, bzbzth	6870 *	595	465
bzSe, ind (VI; Y = Se, Z = CMe_2, R = Me, X = ClO_4)	6115	bzSe, ind	5500	ind, ind	6360 *	615	245
Me-th, bzth	6075	Me-th, bzth	5470	bzth, bzth	6500 *	605	425
Me-th, thiazoline	5050	Me-th, thiazoline	4995	thiazoline, thiazoline	5450 ‡	55	400
Me-th, bzSe	6205	Me-th, bzSe	5510	bzSe, bzSe	6600 *	695	395
thiazoline, 4-q, 4-q	7440	thiazoline, 4-q	5765	4-q, 4-q	8100 *	1675	660
thiazoline, bzth	6070	thiazoline, bzth	5020	bzth, bzth	6500 *	1050	430

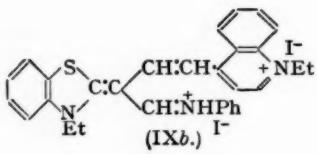
* Fisher and Hamer, *Proc. Roy. Soc.*, 1936, *A*, **154**, 703.
† Beilenson, Fisher, and Hamer, *ibid.*, 1937, *A*, **163**, 138.
‡ Hamer, Rathbone, and Winton, *loc. cit.*

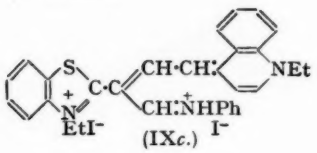
to give (X), of 2-methylbenzthiazole, to give (XI), of a substituted indolenine, and of 2-methyl-Δ^2-thiazoline. In preparing these intermediate *dyes*, temperature was an important controlling factor but their ease of formation varied greatly.

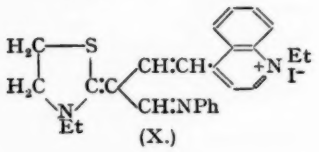

(VIII*a*.)

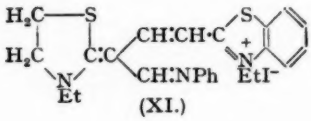

(VIII*b*.)


(IX*a*.)


(IX*b*.)

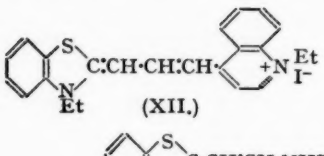

(IX*c*.)

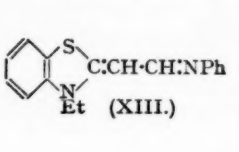

(X.)

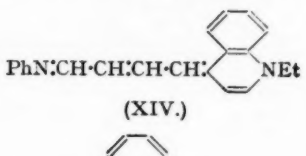

(XI.)

With these intermediate dyes changes of pH produced some striking colour changes. For instance, the blue alcoholic solution of (VIII) became flame-coloured on acidification. For five of the compounds, the pH range of the colour change was determined, but it was concluded that they would be unsatisfactory as indicators because more drastic treatment with acid produced an irreversible change.

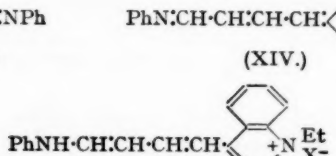
Alkaline methyl-alcoholic solutions of the anilomethyl compounds, as also such acidified solutions, had broader absorption curves than had the neocyanines. It seemed worth comparing the absorption maximum of each new anilomethyl compound with those of the related trimethincyanine, aniloethylidene compound, and anilobutenylidene compound : thus (VIII) would be compared with (XII), (XIII), and (XIV). In addition to this comparison, the absorption maxima of acidified solutions of the twelve *anilomethyl* compounds, represented for


(XII.)


(XIII.)


(XIV.)

(XV.)


(XVI.)

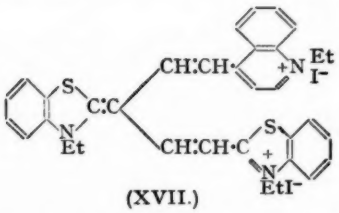
instance by (IX), were compared with acidified methyl-alcoholic solutions of aniloethylidene compounds, such as (XIII), which would contain the corresponding β-anilinovinyl salts, such as (XV) ; they were also compared with acidified solutions of anilobutenylidene compounds, such as (XIV), which would contain the corresponding β-anilinobutadienyl salts, such as (XVI). These comparisons are contained in Table II.

It there appears that on passing from a dinuclear anilomethyl dye, *e.g.*, (VIII), to the corresponding trimethincyanine, *e.g.*, (XII), there was in nine cases a bathochromic shift, varying from 55 to 1080 A., and in three cases a hypsochromic one, varying from 45 to 80 A. : in each of these three the thiazoline nucleus is involved. On passing from three aniloethylidene compounds to the corresponding acid salts, *e.g.*, from (XIII) to (XV), there were two bathochromic shifts and one hypsochromic ; on passing from six anilobutenylidene compounds to the corresponding acid salts, *e.g.*, from (XIV) to (XVI), there was in every instance a bathochromic shift varying from 295 to 715 A. ; with the new anilomethyl dyes, however, *e.g.*, (VIII), the shift on passing from alkaline to acid solution was hypsochromic in ten instances, its amount varying from 110 to 1030 A., and bathochromic, of 95 A. and 450 A., in two. On passing from a mononuclear

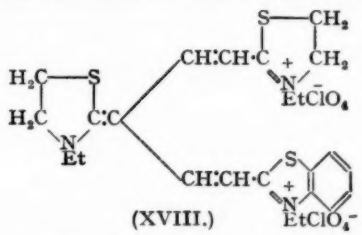
aniloethylidene base, *e.g.*, (XIII), to a dinuclear anilomethyl compound, *e.g.*, (VIII), the shift was always bathochromic, varying in the twelve instances from 80 to 2225 A.; on passing from the mononuclear β-anilinovinyl salt, *e.g.*, (XV), to the corresponding acidified dinuclear intermediate dye, *e.g.*, (IX), there were again twelve bathochromic shifts, varying from 60 to 1290 A. On passing from a mononuclear anilobutenylidene base, *e.g.*, (XIV), to a dinuclear anilomethyl compound, *e.g.*, (VIII), the shift was bathochromic in ten cases, varying from 80 to 1005 A., and hypsochromic in two, of 30 and 35 A.; on passing from the mononuclear β-anilinobutadienyl salt, *e.g.*, (XVI), to the corresponding acidified dinuclear intermediate dye, *e.g.* (IX), all the shifts were hypsochromic, varying from 230 to 710 A.

Through the new type of dye (VIII, etc.) it is possible to arrive at neocyanines of various kinds. In the first place there is afforded an alternative route to neocyanines of the type already described, which have two similar nuclei and one dissimilar, the two similar nuclei being connected by a pentamethin chain. Thus dyes having a Δ^2-thiazoline nucleus at each end of such a chain, and either a benzthiazole or a 4-methylthiazole nucleus in the *meso*-position, were obtained by this route; the absorption data relating to these two dyes have been included in Table I.

Secondly, the new intermediate dyes provide a means of preparing neocyanines, again with two similar nuclei and one dissimilar, but differing from those already described in that the two similar nuclei are connected by a trimethin chain. Thus (XVII), which is the isomeride of (III), was prepared by condensing (VIII) with 2-methylbenzthiazole ethiodide, whilst an



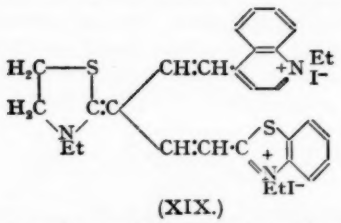
(XVII.)



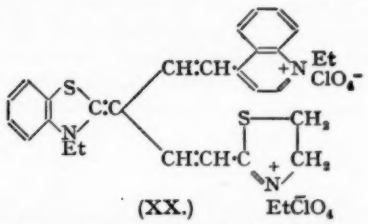
(XVIII.)

analogue having a 2-linked instead of a 4-linked quinolinium nucleus was similarly prepared from the corresponding analogue of (VIII). An analogue of (VIII), having a benzthiazolium in place of the 4-linked quinolinium nucleus, was condensed with 2-methylbenzselenazole ethiodide to give an *analogue* of (XVII) having a benzselenazole in place of the 4-linked quinoline nucleus; an analogue of (VIII) having a Δ^2-thiazolinium in place of the 4-linked quinolinium nucleus, was condensed with 2-methylbenzthiazole ethiodide to give an *analogue* of (XVII), having a thiazolinium in place of the 4-linked quinolinium nucleus. (XVIII) was prepared through the condensation product of (XI) and 2-methyl-Δ^2-thiazoline ethiodide; an *analogue* of (XVIII) having a 4-linked quinolinium in place of the benzthiazolium nucleus was prepared from (X), through condensation with 2-methyl-Δ^2-thiazoline ethiodide.

Thirdly, through the new intermediate dyes there can be obtained neocyanines in which all three nuclei are different. (XIX) was prepared by condensing (X) with 2-methylbenzthiazole ethiodide; (XX), which has the same three nuclei differently arranged, was derived by condensing lepidine ethiodide with an analogue of (VIII), having a thiazoline in place of a lepidine nucleus. A *dye* having a 2-linked quinoline, a 4-linked quinoline, and a benzthiazole nucleus,



(XIX.)



(XX.)

the first and second being at the ends of the pentamethin chain, and the third in the *meso*-position, was prepared, first from (VIII) with quinaldine ethiodide and, secondly, from the analogue of (VIII), having a 2-linked instead of a 4-linked quinolinium nucleus, with lepidine ethiodide. A *dye* having a benzselenazole, a 2-linked quinoline, and a benzthiazole nucleus, the first and second being at the ends of the pentamethin chain, and the third in the *meso*-position, was prepared, first from 2-methylbenzselenazole ethiodide and the analogue of (VIII), having a

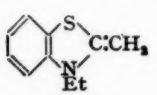
TABLE

Anilomethyl compounds. :C(CH:CH·)(CH:NPh)	Abs. max. (A.) Alkali.	Acid.	Hypsochromic shifts, alkali → acid.	Trimethincyanines. :CH·CH:CH·.	Abs. max. (A.)	Anilethylidene compounds. :CH·CH:NPh.	Abs. max. (A.) Base.	Acid salt.
4-q bzth anMe (VIII)	6030	5000 (IX)	1030	4-q bzth (XII)	6300 ‡	bzth anMe (XIII)	3935 §	4175 § (XV)
2-q bzth anMe	5150	4750	400	2-q bzth	5600 ‡	,,	,,	,,
bzth bzth anMe	5515	4695	820	bzth bzth	5570 ‡	,,	,,	,,
bzSe bzth anMe	4780	4670	110	bzSe bzth	5620 ‡	,,	,,	,,
ind bzth anMe	4350	4800	−450	ind bzth	5430	,,	,,	,,
thiazoline bzth anMe	(4005) 4905	4235	670	thiazoline bzth	5020	,,	,,	,,
4-q Me-th anMe	5720	5010	710	4-q Me-th	6295	Me-th anMe	4090 §	4030 §
2-q Me-th anMe	5060	4815	245	2-q Me-th	5900	,,	,,	,,
thiazoline Me-th anMe	4170	4265	−95	thiazoline Me-th	4995	,,	,,	,,
4-q thiazoline (X) anMe	5810	4950	860	4-q thiazoline	5765	thiazoline anMe	3585 §	3660 §
bzth thiazoline (XI) anMe	5100	4725	375	bzth thiazoline	5020	,,	,,	,,
thiazoline thiazoline anMe	4500	4370	130	thiazoline thiazoline	4435 *	,,	,,	,,

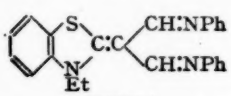
* Brooker, *J. Amer. Chem. Soc.*, 1936, **58**, 662.
† Fisher and Hamer, *Proc. Roy. Soc.*, 1936, *A*, **154**, 703.
‡ Beilenson, Fisher, and Hamer, *ibid.*, 1937, *A*, **163**, 138.
§ Hamer, Rathbone, and Winton, *J.*, 1947, 954, for data about 3-ethyl-2-aniloethylidenebenzthiazoline, 4-methyl-3-ethyl-2-aniloethylidene-Δ^4-thiazoline, 3-ethyl-2-aniloethylidenethiazolidine, and corresponding salts.

2-linked instead of a 4-linked quinoline nucleus and, secondly, from quinaldine ethiodide and the analogue of (VIII), having a benzselenazole instead of a 4-linked quinoline nucleus.

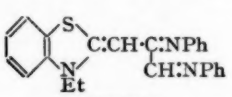
In the first paper of this series (*J.*, 1947, 1434), we felt justified in assuming that when a base such as (XXI) is condensed with ethyl*iso*formanilide, the two anilomethyl groups successively replace the reactive hydrogen atoms of the methylene group to give the dianil, in this case (XXII), the alternative (XXIII) seeming so improbable that the idea could be dismissed. Structures such as (XXIII) are now definitely disproved by two facts : first, that when a dianil



(XXI.)



(XXII.)



(XXIII.)

is caused to react with one molecular proportion of a heterocyclic quaternary ammonium salt, having a reactive methyl group, only one intermediate dye has ever been obtained, whereas formula (XXIII) for the dianil could lead to two; secondly, that when neocyanines having three different nuclei have been synthesised, the order of introduction of the second and the third

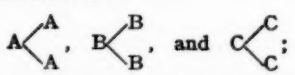
II.

Bathochromic shifts, base → salt.	Anilobutenylidene compounds. CH:CH·CH: CH:NPh	Abs. max. (A.) Base.	Salt.	Bathochromic shifts, base → salt.	Bathochromic shifts. AniloMe Base → trimethincyanine.	Bases: Anilethylidene → AniloMe.	Salts: Anilethylidene → AniloMe.	Bases: Anilobutenylidene → AniloMe.	Salts: Anilobutenylidene → AniloMe.
240	4-q anMe (XIV)	5355 ‖	5660 ‖ (XVI)	305	270	2095	825	675	−660
,,	2-q anMe	4980 ‖	5275 ‖	295	450	1215	575	170	−525
,,	bzth anMe	4510 ‖	5120 ‖	610	55	1580	520	1005	−425
,,	bzSe anMe	4505 ‖	5220 ‖	715	840	845	495	275	−550
,,	ind anMe	4385 ‖	5090 ‖	705	1080	415	625	−35	−290
,,	thiazoline anMe	4200 ‖	4600 ‖	400	115	970	60	705	−365
−60	4-q anMe	5355 ‖	5660 ‖	305	575	1630	980	365	−650
,,	2-q anMe	4980 ‖	5275 ‖	295	840	970	785	80	−460
,,	thiazoline anMe	4200 ‖	4600 ‖	400	825	80	235	−30	−335
75	4-q anMe	5355 ‖	5660 ‖	305	−45	2225	1290	455	−710
,,	bzth anMe	4510 ‖	5120 ‖	610	−80	1515	1065	590	−395
,,	thiazoline anMe	4200 ‖	4600 ‖	400	−65	915	710	300	−230

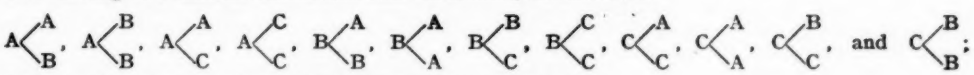
‖ Hamer, *J.*, in the press, for data about 4 (and 2)-(4′-anilino-buta-1′ : 3′-dienyl)quinoline ethoperchlorate, 2-(4′-anilino-buta-1′ : 3′-dienyl)benzthiazole (and benzselenazole) ethoperchlorate, 2-(4′-anilino-buta-1′ : 3′-dienyl)-3 : 3-dimethylindolenine methoperchlorate, 2-(4′-anilino-buta-1′ : 3′-dienyl)-Δ^2-thiazoline ethiodide, and corresponding bases.

nucleus has been immaterial, which can only be explained by the dianil having the symmetrical structure (XXII).

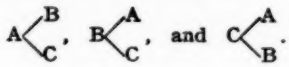
Clearly, our new synthetic methods afford the possibility of preparing countless new dyes. Thus taking three nuclei, A, B, and C, eighteen different dyes are theoretically possible, *viz.*, three having three similar nuclei, indicated as



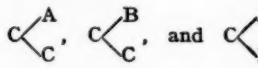
twelve having two similar nuclei and one dissimilar, indicated as



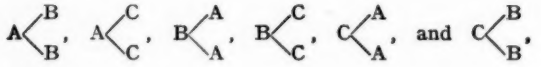
and lastly three having three dissimilar nuclei, indicated as



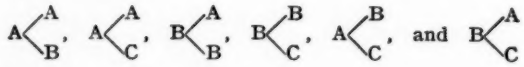
The preparation of a whole such set of eighteen dyes seemed attractive. In choosing three suitable nuclei, we decided on Δ^2-thiazoline (A), benzthiazole (B), and 4-linked quinoline (C), because the first nucleus tends to push the absorption maximum towards the most refrangible, and the last towards the least refrangible region, whilst the benzthiazole nucleus has an intermediate effect. Evidence has been adduced to show that, of these three nuclei, the Δ^2-thiazoline is the least basic and the 4-linked quinoline the most (Brooker, Sklar, Cressman, Keyes, Smith, Sprague, Van Larc, Van Zandt, White, and Williams, *J. Amer. Chem. Soc.*, **1945**, **67**, 1875). The first three dyes have already been described in the first paper of this series (*loc. cit.*), and twelve others are described here. The three



are missing, owing to the difficulty of preparing a pure anilomethyl intermediate dye from (I). The absorption data for



are given in Table I, whilst those for



are given, together with others, in Table III.

The ten neocyanines of Table III differ from those of Table I in having two different nuclei attached to that in the *meso*-position. Whereas the absorption maximum of each neocyanine of Table I was compared with that of an unsymmetrical trimethincyanine and a symmetrical pentamethincyanine, each neocyanine of Table II is compared with two trimethincyanines, of which at least one is unsymmetrical, and with an unsymmetrical pentamethincyanine. Some of the parent pentamethincyanines required for the comparisons in Table III, as also the anilobutenylidene compounds required for those in Table II, are not described in the literature and were therefore prepared (Hamer, *J.*, in the press). Of the twenty shifts on passing from trimethincyanine to neocyanine, nineteen were bathochromic, varying from 10 to 1615 A., and one hypsochromic, of 310 A. Of the ten shifts on passing from neocyanine to pentamethincyanine, all were bathochromic, varying from 425 to 875 A.

Unless otherwise stated, the absorption maxima recorded are those of methyl-alcoholic solutions, and the photographic tests were carried out with gelatino-bromide plates. In view of the fact that the first neocyanine was described as the best infra-red sensitiser of its time (Dundon, Schoen, and Briggs, *J. Opt. Soc. Amer.*, **1926**, **12**, 397), it may seem surprising that some of the new neocyanines confer little or no extra-sensitivity, whilst decreasing the normal blue sensitivity of the photographic plate. A partial explanation is the fact that meanwhile standards of comparison of infra-red sensitisers have been raised, by the discovery of the pentamethincyanines (I.C.I. Ltd., Piggott, and Rodd, B.P. 355,693/1930), heptamethincyanines (Fisher and Hamer, *J.*, **1933**, 189), etc. Our anilomethyl intermediate dyes comprise photographic sensitisers.

Nomenclature.—In the experimental section of this paper, the nomenclature used is that explained in Part I (*loc. cit.*). The shorter methin chain is taken as the fundamental one, the α, β, γ . . . running from the system named first to that named second. The side chain has α', β', γ' . . . with α' attached to the system named third.

Experimental.

[2-(1-*Ethylquinoline*)][4-(1-*ethylquinoline*)][$\gamma\beta'$-*dimethin*-2′-(1′-*ethylquinoline*)]*trimethincyanine Diiodide* (II.)—Crude 1-ethyl-4-dianilo*iso*propylidene-1 : 4-dihydroquinoline (I) (0·75 g.; 1 mol.), quinaldine ethiodide (1·20 g.; 2 mols.), anhydrous sodium acetate (1·31 g.; 8 mols.), and acetic anhydride (8 c.c.) were heated together in a glycerol-bath at 135—140° for 10 minutes. After cooling with ice, the solid was filtered off, washed with acetic anhydride and then with ether, ground with water (15 c.c.), and washed thrice with methyl alcohol. The crude dye (0·48 g.; 31% yield) was recrystallised from methyl alcohol (90 c.c. per g.) and thus obtained in 24% yield. A specimen was dried in a vacuum at 60—80° and analysed by the method of Carius, which methods of drying and analysis were used throughout this work (Found : I, 32·35. $C_{38}H_{37}N_3I_2$ requires I, 32·15%). The greenish-gold crystals gave off solvent from about 120°; shrinking began at about 190°, m. p. 264° (decomp.). The absorption curve had its maximum at 6725 A. and an inflexion at 6200 A. Towards a photographic emulsion the *dye* showed desensitising but no sensitising action.

TABLE III.

Neocyanines.	Abs. max. (A.)	Trimethincyanines.	Abs. max. (A.)	Pentamethincyanines.	Abs. max. (A.)	Bathochromic shifts. Trimethin- to neocyanine.	Bathochromic shifts. Neo- to pentamethincyanine.
bzth, bzth, 4-q (XVII)	6480	bzth, bzth	5570 *	bzth, bzth, 4-q	7250 ‡	910	770
		bzth, 4-q	6300 ‡			180	
bzth, bzth, 2-q	6110	bzth, bzth	5570 *	bzth, bzth, 2-q	6760 ‡	540	650
		bzth, 2-q	5600 ‡			510	
bzth, bzth, bzSe	6100	bzth, bzth	5570 *	bzth, bzth, bzSe	6590 ‡	530	490
		bzth, bzSe	5620 ‡			480	
bzth, bzth, thiazoline	5580	bzth, bzth	5570 *	bzth, bzth, thiazoline	6005 §	10	425
		bzth, thiazoline	5020			560	
bzth, 4-q, 2-q	6730	bzth, 4-q	6300 ‡	4-q, 4-q, 2-q	7605 §	430	875
		bzth, 2-q	5600 ‡			1130	
bzth, 4-q, thiazoline (XX)	5990	bzth, 4-q	6300 ‡	4-q, 4-q, thiazoline	6705 §	−310	715
		bzth, thiazoline	5020			970	
bzth, 2-q, bzSe	6260	bzth, 2-q	5600 ‡	2-q, 2-q, bzSe	6750 ‡	660	490
		bzth, bzSe	5620 ‡			640	
thiazoline, thiazoline, 4-q	6050	thiazoline, thiazoline	4435 †	thiazoline, thiazoline, 4-q	6705 §	1615	655
		thiazoline, 4-q	5765			285	
thiazoline, thiazoline, bzth (XVIII)	5580	thiazoline, thiazoline	4435 †	thiazoline, thiazoline, bzth	6005 §	1145	425
		thiazoline, bzth	5020			560	
4-q, thiazoline, bzth (XIX)	6555	4-q, thiazoline	5765	4-q, 4-q, bzth	7250 ‡	790	695
		thiazoline, bzth	5020			1535	

* Fisher and Hamer, *Proc. Roy. Soc.*, 1936, *A*, **154**, 703.
† Brooker, *J. Amer. Chem. Soc.*, 1936, **58**, 662.
‡ Beilenson, Fisher, and Hamer, *Proc. Roy. Soc.*, 1937, *A*, **163**, 138.
§ Hamer, *J.*, in the press.

[4-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)][αβ′-*dimethin*-2′-(3′-*ethylbenzthiazole*)]*trimethincyanine Di-iodide* (III.)—Crude 1-ethyl-4-dianilo*iso*propylidene-1 : 4-dihydroquinoline (I) (0·38 g.; 1 mol.), 2-methylbenzthiazole ethiodide (0·62 g.; 2 mols.), and pyridine (2 c.c.) were heated together at 115—122° for 5 minutes. The *dye* was filtered off and washed with pyridine and with ether; yield 59% (0·48 g.). After recrystallisation from methyl alcohol (115 c.c. per g.), the yield was 31% (Found: I, 31·65. $C_{34}H_{33}N_3I_2S_2$ requires I, 31·7%). The green crystals had m. p. 281° (decomp.), and desensitised, without sensitising, a photographic emulsion. The absorption curve had its maximum at 6320 A.

When heating for 10 minutes at 135—140° with sodium acetate and acetic anhydride took the place

of condensation by means of pyridine, the yields of crude and recrystallised dye were 56% and 42%, respectively.

[2-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)][αβ′-*dimethin*-2′-(3′-*ethylbenzthiazole*)]*trimethincyanine Di-iodide*.—Crude 1-ethyl-2-dianilo*iso*propylidene-1 : 2-dihydroquinoline (0·69 g.) was condensed with 2-methylbenzthiazole ethiodide in pyridine. The washed dye (0·47 g.) was recrystallised from methyl alcohol (45 c.c.; 32% yield), ground with water (5 c.c.; 28% yield), and again recrystallised from methyl alcohol (30 c.c.; 19% yield) (Found: I, 31·5. $C_{34}H_{33}N_3I_2Se$ requires I, 31·7%). The dark green crystals had m. p. 255° (decomp.). The absorption maximum was at 6180 A. The *substance* showed slight desensitisation.

[4-(1-*Ethylquinoline*)][2-(3-*ethyl*-Δ^2-*thiazoline*)][αβ′-*dimethin*-2′-(3′-*ethyl*-$\Delta^{2'}$-*thiazoline*)]*trimethincyanine Diperchlorate* (IV).—The reaction mixture from the heating of crude 1-ethyl-4-dianilo*iso*propylidene-1 : 4-dihydroquinoline (I) (0·75 g.) with 2-methyl-Δ^2-thiazoline ethiodide, anhydrous sodium acetate, and acetic anhydride, was treated with absolute ether. The solid was filtered off, washed with ether, and treated with cold water (20 c.c.); this was decanted off from the resultant red tar, which was further washed with water (20 c.c.). On treating its solution in hot methyl alcohol (12 c.c.) with one of sodium perchlorate (1·47 g.; 6 mols.) in water (12 c.c.), the dye *perchlorate* crystallised (38% yield); after recrystallisation from methyl alcohol, the yield was 12% and after a second recrystallisation (230 c.c. per g.) 6% (Found: Cl, 11·1. $C_{26}H_{33}O_4N_3Cl_2S_2$ requires Cl, 10·9%). The dark blue crystals melted at about 260° (decomp.). Their absorption maximum was at 5270 A. The substance slightly depressed the sensitivity of a photographic emulsion.

[4-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)][γβ′-*dimethin*-4′-(1′-*ethylquinoline*)]*trimethincyanine Di-iodide* (V).—3-Ethyl-2-dianilo*iso*propylidenebenzthiazoline (0·77 g.; 1 mol.), lepidine ethiodide (1·20 g.; 2 mols.), anhydrous sodium acetate (0·66 g.; 4 mols.), and acetic anhydride (4 c.c.) were heated together at 140—150° for 5 minutes. Precipitation with absolute ether (20 c.c.) was effected and the solid was washed with ether. On grinding with water (5 c.c.), it became tarry, but heating the tar with methyl alcohol (10 c.c.) caused it to crystallise. The yield of washed dye was 67% (1·07 g.). By boiling out with, and recrystallising from, methyl alcohol (5 c.c., 25 c.c.), it was obtained in 46% yield (Found: I, 32·15. $C_{36}H_{35}N_3I_2S$ requires I, 31·9%). The coppery crystals had m. p. 221° (decomp.). The absorption maximum was at 7200 A. The *dye* gave no photographic sensitation but desensitised strongly.

Attempts to prepare this dye by use of pyridine gave a product of lower iodine content, which was recognised as its mixture with the anilomethyl intermediate. Further heating of the mixed dyes with lepidine ethiodide, sodium acetate, and acetic anhydride yielded (V).

[2-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)][γβ′-*dimethin*-2′-(1′-*ethylquinoline*)]*trimethincyanine Di-iodide*.—3-Ethyl-2-dianilo*iso*propylidenebenzthiazoline (0·77 g.) and quinaldine ethiodide were heated together in pyridine (4 c.c.). The dye was precipitated with absolute ether (20 c.c.) and heated with methyl alcohol (10 c.c.). The yield was 33%. It was boiled out with, and recrystallised from, methyl alcohol (9 c.c. per g., 85 c.c. per g.) and thus obtained in 23% yield (Found: I, 32·0. $C_{36}H_{35}N_3I_2S$ requires I, 31·9%). The green crystals had m. p. about 249° (decomp.) but depending on the rate of heating. The absorption maximum was at 6365 A. with an inflexion to the curve at about 5870 A. The *dye* sensitised weakly from 6600 to 6900 A.

[2-(3-*Ethylbenzoxazole*)][2-(3-*ethylbenzthiazole*)][γβ′-*dimethin*-2′-(3′-*ethylbenzoxazole*)]*trimethincyanine Di-iodide* (VI; Y = S, Z = O, R = Et, X = I).—3-Ethyl-2-dianilo*iso*propylidenebenzthiazoline (0·77 g.), 2-methylbenzoxazole ethiodide, and pyridine (4 c.c.) were heated together at 130—135° for 2 minutes and the *product* was precipitated with ether (30 c.c.). By heating with methyl alcohol (4 c.c.) it was obtained crystalline in 56% yield (0·87 g.). It was boiled out with, and recrystallised from, methyl alcohol (5 c.c., 25 c.c.), resulting in 31% yield. After a second recrystallisation (42 c.c. per g.), the yield was 23% (Found: I, 32·6. $C_{32}H_{31}O_2N_2IS$ requires I, 32·75%). The bronze crystals had m. p. 236° (decomp.) and sensitised weakly from 5600 to 6000 A., whilst depressing the normal blue sensitivity of the plate. The absorption curve had its maximum at 5400 A. with an inflexion at 5000 A.

[2-(3-*Ethyl*-6 : 7-*benzbenzoxazole*)][2-(3-*ethyl*-6 : 7-*benzbenzthiazole*)][γβ′-*dimethin*-2′-(3′-*ethyl*-6′ : 7′-*benzbenzthiazole*)]*trimethincyanine Di-iodide* (VII).—3-Ethyl-2-dianilo*iso*propylidene-6 : 7-benzbenzthiazoline (0·58 g.) and 2-methyl-6 : 7-benzbenzoxazole ethiodide were similarly heated in pyridine. The *product* which separated (1·04 g.) was boiled out with methyl alcohol (10 c.c.), and the residue then boiled out twice more with methyl alcohol (25 c.c. × 2, giving 0·05 g.) and once with pyridine (15 c.c., giving 0·01 g.). The undissolved residue (0·55 g.) was added to what had crystallised (0·06 g.), making a 49% yield (Found: I, 27·3. $C_{44}H_{37}O_2N_3I_2S$ requires I, 27·45%). The purple crystals had m. p. at about 238° (decomp.). The absorption maximum was at 5700 A. There was weak sensitisation to 6700 A. with decrease of the normal blue speed of the plate.

[2-(3-*Ethylbenzthiazole*)][2-(3-*ethylbenzselenazole*)][αβ′-*dimethin*-2′-(3′-*ethylbenzselenazole*)]*trimethincyanine Di-iodide* (VI; Y = S, Z = Se, R = Et, X = I).—This was similarly prepared from 3-ethyl-2-dianilo*iso*propylidenebenzthiazoline and 2-methylbenzselenazole ethiodide, with heating for 5 minutes (83% yield). After recrystallisation from methyl alcohol (440 c.c. per g.), the yield was 48% (Found: I, 28·05. $C_{32}H_{31}N_3I_2SSe_2$ requires I, 28·15%). The dark green crystals had m. p. about 235° (decomp.), with previous softening, but dependent upon the rate of heating. The absorption maximum was at 6155 A. with a secondary maximum at 5580 A. The *dye* showed no sensitising but only desensitising properties.

[2-(1-*Ethylquinoline*)][2-(3-*ethylbenzselenazole*)][γβ′-*dimethin*-2′-(1′-*ethylquinoline*)]*trimethincyanine Di-iodide*.—3-Ethyl-2-dianilo*iso*propylidenebenzselenazoline (1·72 g.; 1 mol.), quinaldine etho-*p*-toluenesulphonate (3·42 g.; 2·5 mols.), anhydrous sodium acetate (1·32 g.; 4 mols.), and acetic anhydride (30 c.c.) were heated together at 145—150° for 5 minutes. The hot reaction mixture was treated with a solution of potassium iodide (5·6 g.; 8 mols.) in water (200 c.c.). The crude dye (0·7 g.) was twice boiled out with methyl alcohol (10 c.c. × 2) and the residue then recrystallised from it (75 c.c.), giving an 8% yield (Found: I, 30·25. $C_{36}H_{35}N_3I_2Se$ requires I, 30·15%). The green and gold crystals had m. p. 235° (decomp.). The absorption curve had its maximum at 6435 A. The *dye* desensitised and did not sensitise.

[2-(3-*Ethylbenzoxazole*)][2-(3-*ethylbenzselenazole*)][γβ′-*dimethin*-2′-(3′-*ethylbenzoxazole*)]*trimethincyanine Di-iodide* (VI; Y = Se, Z = O, R = Et, X = I).—Prepared by heating together 3-ethyl-2-dianilo-*iso*propylidenebenzselenazoline (1·72 g.), 2-methylbenzoxazole ethiodide, and pyridine, this *dye* was precipitated by absolute ether and treated with water, being obtained in 57% yield. It was boiled out with absolute alcohol (10 c.c.) and fractionally crystallised from methyl alcohol (10 c.c., 35 c.c.). The solid (0·16 g.) from the second fraction gave an orange spirit solution and was rejected. That from the first (0·48 g.) and a second crop from it (0·54 g.) were combined, making a 31% yield) (Found: I, 31·0. $C_{33}H_{31}O_2N_3I_2Se$ requires I, 30·85%). The dark red crystals had m. p. 215° (decomp.). The absorption maximum was at 5465 A. with an inflexion to the curve at about 5150 A. The substance sensitised weakly from 5400 to 6100 A. with the maximum at 5850 A. It depressed the normal blue sensitivity.

[2-(3-*Ethylbenzthiazole*)][2-(3-*ethylbenzselenazole*)][γβ′-*dimethin*-2′-(3′-*ethylbenzthiazole*)]*trimethincyanine Di-iodide* (VI; Y = Se, Z = S, R = Et, X = I).—Prepared by heating together 3-ethyl-2-dianilo*iso*propylidenebenzselenazoline, 2-methylbenzthiazole ethiodide, and pyridine, some *dye* crystallised on cooling and more was precipitated by absolute ether (total yield 86%). Recrystallisation from methyl alcohol (80 c.c. per g.) gave a 66% yield (Found: I, 29·85. $C_{33}H_{31}N_3I_2S_2Se$ requires I, 29·7%). The dark green crystals had m. p. 235° (decomp.). The absorption maximum was at 6085 A. with a slight inflexion to the curve at about 6600 A. The dye imparted no extra photographic sensitivity but caused some depression of the normal blue sensitivity.

[2-(3-*Ethyl*-6 : 7-*benzbenzthiazole*)][2-(3-*ethylbenzselenazole*)][γβ′-*dimethin*-2′-(3′-*ethyl*-6′ : 7′-*benzbenzthiazole*)]*trimethincyanine Di-iodide*.—3-Ethyl-2-dianilo*iso*propylidenebenzselenazoline (0·86 g.), 2-methyl-6 : 7-benzbenzthiazole etho-*p*-toluenesulphonate, and pyridine were heated together and the reaction mixture treated hot with an aqueous potassium iodide solution. The washed dye iodide (1·7 g.) was boiled out with methyl alcohol (25 c.c.) and the residual solid (1·4 g.) fractionally crystallised from methyl alcohol (50 c.c., 155 c.c.). The second fraction (0·58 g.) consisted of bronze crystals giving a pure blue solution. The first fraction (0·5 g.) was given a second crystallisation from methyl alcohol (25 c.c.; 0·2 g. obtained). The total yield (0·78 g.) was 41% (Found: I, 26·4. $C_{40}H_{35}N_3I_2S_2Se$ requires I, 26·6%. The *dye*, m. p. 193° (decomp.), did not sensitise but depressed the blue sensitivity. The absorption maximum was at 6405 A. and the curve had a faint inflexion in the more refrangible region.

[2-(1 : 3 : 3-*Trimethylindolenine*)][2-(3-*ethylbenzselenazole*)][γβ′-*dimethin*-2′-(1′ : 3′ : 3′-*trimethylindolenine*)]*trimethincyanine Diperchlorate* (VI; Y = Se, Z = CMe_2, R = Me, X = ClO_4).—3-Ethyl-2-dianilo*iso*propylidenebenzselenazoline (1·08 g.; 1 mol.) and 2 : 3 : 3-trimethylindolenine methiodide (1·51 g.; 2 mols.) did not condense in pyridine. After they had been boiled with acetic anhydride (20 c.c.) and anhydrous sodium acetate (2·44 g.; 8 mols.) for 3 minutes, the mixture was poured into a hot solution of sodium perchlorate (2·8 g.; 8 mols.) in water (100 c.c.). The dye perchlorate (73% yield, 1·45 g.) was fractionally recrystallised from absolute ethyl alcohol (8 c.c.×2) and methyl alcohol (8 c.c., 23 c.c., 65 c.c.). The third fraction (0·1 g.) was discarded. The fourth and fifth amounted to a 24% yield (0·48 g.) of dark bluish-green crystals, m. p. 252° (decomp.) (Found: Cl, 9·1. $C_{36}H_{39}O_8N_3Cl_2Se$ requires Cl, 8·95%). The absorption maximum was at 6115 A. with a secondary maximum at 5720 A. The *dye* did not sensitise but considerably depressed blue sensitivity. It was accompanied by more soluble, dark purple crystals (0·39 g.), obtained from the first two fractions (Found: Cl, 7·2. $C_{23}H_{25}O_4N_2ClSe$ requires Cl, 7·0%). By the analysis, and by m. p. and mixed m.p., this by-product was identified as the *carbocyanine*, which was synthesised for comparison, and is described at the end of the paper (p. 1887).

[2-(4-*Methyl*-3-*ethylthiazole*)][2-(3-*ethylbenzthiazole*)][αβ′-*dimethin*-2′-(3′-*ethylbenzthiazole*)]*trimethincyanine Di-iodide*.—When 4-methyl-3-ethyl-2-dianilo*iso*propylidene-Δ^4-thiazoline (0·7 g.), 2-methylbenzthiazole ethiodide, and pyridine were heated together, dye crystallised (86% yield). After boiling out with, and recrystallising from, methyl alcohol (15 c.c. per g., 280 c.c. per g.), it was obtained in 57% yield (Found: I, 32·8. $C_{29}H_{31}N_3I_2S_2$ requires I, 32·9%). The green and gold crystals had m. p. 247° (decomp.). Their methyl-alcoholic solution was blue by transmitted and purple by reflected light. The absorption maximum was at 6075 A., and the curve had an inflexion at 5600 A. The *dye* sensitised weakly from 5700 to 6900 A., with the maximum at 6500 A., and depressed blue sensitivity.

[2-(4-*Methyl*-3-*ethylthiazole*)][2-(3-*ethylbenzselenazole*)][αβ′-*dimethin*-2′-(3′-*ethylbenzselenazole*)]*trimethincyanine Di-iodide*.—This was similarly prepared by use of 2-methylbenzselenazole ethiodide. The crude product (77% yield), after recrystallisation from methyl alcohol (240 c.c. per g.), was obtained in 61% yield (Found: I, 29·3. $C_{29}H_{31}N_3I_2SSe_2$ requires I, 29·35%), as emerald-green crystals with a golden reflex. They melted at 230° (decomp.). The absorption maximum was at 6205 A. with an inflexion to the curve at 5750 A. The *substance* sensitised weakly from 6300 to 6800 A., with the maximum at 6700 A., and depressed blue sensitivity.

[4-(1-*Ethylquinoline*)][2-(3-*ethyl*-Δ^2-*thiazoline*)][γβ′-*dimethin*-4′-(1′-*ethylquinoline*)]*trimethincyanine di-iodide* was prepared by heating together 3-ethyl-2-dianilo*iso*propylidenethiazolidine (1·12 g.; 1 mol.), lepidine ethiodide, anhydrous sodium acetate (4 mols.), and acetic anhydride at 130—140° for 2 minutes. It crystallised and was washed, then was boiled out with, and recrystallised from, methyl alcohol (10 c.c., 550 c.c.), being obtained in 37% yield (Found: I, 34·0. $C_{29}H_{35}N_3I_2S$ requires I, 33·95%). The golden crystals melted at 272° (decomp.). Their absorption maximum was at 7440 A. The compound fogged a photographic plate and decreased its sensitivity.

[2-(3-*Ethyl*-Δ^2-*thiazoline*)][2-(3-*ethylbenzthiazole*)][αβ′-*dimethin*-2′-(3′-*ethylbenzthiazole*)]*trimethincyanine Di-iodide*.—This was prepared by heating together 3-ethyl-2-dianilo*iso*propylidenethiazolidine (1·12 g.), 2-methylbenzthiazole ethiodide, and pyridine. It crystallised on cooling and the washed product was boiled out with, and recrystallised from, methyl alcohol (10 c.c., 1070 c.c.) and gave a 79% yield (Found: I, 33·35. $C_{29}H_{31}N_3I_2S_3$ requires I, 33·45%). The green and gold crystals had m. p. 237° (decomp.). The absorption maximum was at 6070 A. The *dye* decreased the normal blue sensitivity of a photographic emulsion, while conferring weak sensitisation from 5500 to 6800 A.

[4-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)]-γ-*anilomethyltrimethincyanine Iodide* (VIII).—3-Ethyl-2-dianilo*iso*propylidenebenzthiazoline (3·07 g.; 1 mol.), lepidine ethiodide (2·40 g.; 1 mol.), and pyridine

(16 c.c.) were heated together for 10 minutes at 60—70°. The *dye* was precipitated with absolute ether (160 c.c.), well washed with water, and washed with ether in a Soxhlet apparatus (4·17 g. left; 88% yield). On recrystallisation from methyl alcohol (100 c.c. per g.) it resulted in 71% yield (Found: I, 21·45. $C_{30}H_{28}N_2IS$ requires I, 21·55%). The dark green powder had m.p. 218—219° (decomp.). The methyl-alcoholic solution was orange-red at pH 8·0 and violet-blue at pH 9·4. The absorption maximum of a methyl-alcoholic solution containing ammonia was at 6030 A. and of one containing sulphuric acid at 5000 A., this curve showing an inflexion at 4710 A. The substance was a photographic desensitiser.

[2-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)]-*γ-anilomethyltrimethincyanine iodide* was similarly prepared, with quinaldine ethiodide in place of lepidine ethiodide (67% yield after Soxhlet extraction). After recrystallising from methyl alcohol (35 c.c. per g.), grinding with water, and again recrystallising, the yield was 32% (Found: I, 21·65. $C_{30}H_{26}N_2IS$ requires I, 21·55%). The m. p. of the extremely dark maroon crystals was dependent on the rate of heating and was about 210° (decomp.). A methyl-alcoholic solution was crimson at pH 8·6 and bright yellow at pH 7·4. One containing ammonia had its absorption maximum at 5150 A., whilst one containing sulphuric acid had a narrower curve, with its maximum at 4750 A. There was weak sensitisation, with the maximum at 6000 A., and strong blue depression.

The preparation could be effected in boilding absolute alcohol for 1 minute, instead of in pyridine at 60—70° for 10 minutes.

[*Bis*-2-(3-*ethylbenzthiazole*)]-*α-anilomethyltrimethincyanine Iodide*.—This preparation was carried out as for (VIII) but with 2-methylbenzthiazole ethiodide instead of lepidine ethiodide. After Soxhlet extraction, the undissolved residue (94% yield) was recrystallised from methyl alcohol (23 c.c. per g.), ground with water and again thus recrystallised (30 c.c. per g.), giving a 41% yield (Found: I, 21·4; S, 10·55. $C_{28}H_{26}N_2IS_2$ requires I, 21·3; S, 10·75%). The dark maroon powder had an indefinite m. p., at about 210° (decomp. from 180°). A methyl-alcoholic solution was red at pH 7·8 and lemon-yellow at pH 6·8. One containing ammonia faded rapidly in the light but one containing pyridine had its absorption maximum at 5515 A. and one containing sulphuric acid at 4695 A. There was no sensitisation, but depression of the normal blue sensitivity by the *dye*.

[2-(3-*Ethylbenzthiazole*)][2-(3-*ethylbenzselenazole*)]-*α-anilomethyltrimethincyanine Iodide*.—A mixture of 3-ethyl-2-dianil*oiso*propylidenebenzthiazoline (1·92 g.), 2-methylbenzselenazole ethiodide, and pyridine was heated at 50—60° for 10 minutes. The liquid was treated with absolute ether (100 c.c.), and the sticky solid was filtered off, ground with benzene (50 c.c.), and twice extracted with hot water (500 c.c. × 2). The residual *dye* (2·44 g.; 76% yield) was first recrystallised from pyridine and water (24 c.c. of each; 58% yield), next boiled out with, and recrystallised from, methyl alcohol (10 c.c., 110 c.c.), and finally twice more recrystallised from methyl alcohol (65 c.c. per g.), giving a 24% yield (Found: I, 19·5. $C_{28}H_{26}N_2ISSe$ requires I, 19·75%). The maroon solid had m. p. about 198—204° (decomp.). A methyl-alcoholic solution containing ammonia had its maximum at 4780 A.; one containing sulphuric acid had the maximum at 4670 A. with a secondary one at 5455 A. There was very weak sensitisation up to 5700 A.

[2-(1 : 3 : 3-*Trimethylindolenine*)][2-(3-*ethylbenzthiazole*)]-*γ-anilomethyltrimethincyanine Perchlorate*.—3-Ethyl-2-dianil*oiso*propylidenebenzthiazoline (1·54 g.; 1 mol.) and 2 : 3 : 3-trimethylindolenine methiodide (1·22 g.; 1 mol.), mixed with pyridine (20 c.c.), were kept at room temperature for 4½ hours. The tar precipitated by anhydrous ether (100 c.c.) was taken up in methyl alcohol (20 c.c.) and added to a hot solution of sodium perchlorate (1·23 g.; 5 mols.) in water (50 c.c.). The solid was filtered off, washed, and again dissolved in methyl alcohol and treated with sodium perchlorate solution. The *product* (1·88 g.) was fractionally recrystallised from spirit (5 c.c., 7 c.c., 10 c.c. × 2, 15 c.c.). The crystals from the three intermediate fractions (0·69 g.), together with a second crop (0·12 g.) obtained by concentration of the filtrates, amounted to a 36% yield (0·81 g.). This was again fractionated with spirit (5 c.c., 10 c.c.×2), the first two fractions giving a 19% yield (0·43 g.) (Found: Cl, 6·55. $C_{30}H_{29}O_4N_2ClS$ requires Cl, 6·3%). The dark bronze powder melted at about 123—128° (decomp.). The absorption maximum of a methyl-alcoholic solution containing ammonia was at 4350 A. and of one containing sulphuric acid at 4800 A., with an inflexion to the curve at 5400 A. There was very weak sensitisation from 5300 to 5900 A., with slight depression of the normal sensitivity.

[2-(3-*Ethyl*-Δ^2-*thiazoline*)][2-(3-*ethylbenzthiazole*)]-*γ-anilomethyltrimethincyanine Iodide*.—3-Ethyl-2-dianil*oiso*propylidenebenzthiazoline (0·77 g.; 1 mol.) and 2-methyl-Δ^2-thiazoline ethiodide (0·62 g.; 1·2 mols.) were stirred together in ice-cold pyridine (4 c.c.). After 6 hours in ice, the red solution was treated with ice-cold water (32 c.c.). The resultant red oil solidified and was washed (88% yield, 0·97 g.). The yield was 66% after one recrystallisation from absolute ethyl alcohol (15 c.c.) and 56% after a second (Found: S, 11·5. $C_{24}H_{26}N_2IS_2$ requires S, 11·7%). The bright red crystals began to shrink at about 80° and to darken at about 100°; there was considerable decomposition from 125° to 130° but no definite m. p. A methyl-alcoholic solution containing pyridine had absorption maxima at 4005 and 4905 A. One containing sulphuric acid had the maximum at 4235 A. The *dye* weakly sensitised a gelatino-chloride photographic emulsion to 5000 A., the maximum lying at 4500 A.

[4-(1-*Ethylquinoline*)][2-(4-*methyl*-3-*ethylthiazole*)]-*γ-anilomethyltrimethincyanine Iodide*.—4-Methyl-3-ethyl-2-dianil*oiso*propylidene-Δ^4-thiazoline (1·16 g.; 1 mol.), lepidine ethiodide (1·0 g.; 1 mol.), and pyridine (15 c.c.) were heated together at 100° for 4 minutes. The dye was precipitated with ether, washed with water, recrystallised from methyl alcohol (50 c.c.), and obtained in 57% yield (Found: I, 23·1. $C_{27}H_{28}N_2IS$ requires I, 22·95%). The dark green crystals had m. p. 211° (decomp.). A methyl-alcoholic solution was purple at pH 10·1 and reddish-orange at pH 8·7. One containing ammonia had its absorption maximum at 5720 A., with an inflexion to the curve at 5410 A., and one containing sulphuric acid had its maximum at 5010 A. The *substance* sensitised weakly to 5500 A., with slight depression of the normal sensitivity.

[2-(1-*Ethylquinoline*)][2-(4-*methyl*-3-*ethylthiazole*)]-*γ-anilomethyltrimethincyanine Iodide*.—This was similarly prepared from the dianilo-compound (1·16 g.) with quinaldine etho-*p*-toluenesulphonate, instead of lepidine ethiodide, and the crude dye was precipitated with ether. The resultant sticky solid

was dissolved in hot spirit and converted into dye iodide by treatment with aqueous potassium iodide solution. The *iodide* was recrystallised from methyl alcohol (15 c.c.; 0·64 g. obtained), and then again (10 c.c.), a little neocyanine being left undissolved, and the yield was 28% (Found: I, 23·1. $C_{27}H_{28}N_3IS$ requires I, 22·95%). The purple crystals had m. p. 217° (decomp.). A methyl-alcoholic solution was brick-red at pH 9·2 and orange-yellow at pH 8·0. One containing ammonia had its absorption maximum at 5060 A., and one containing sulphuric acid at 4815 A. On a gelatino-chloride photographic emulsion the dye conferred sensitivity extending to 5900 with the maximum at 5250 A.

[2-(3-*Ethyl*-Δ^2-*thiazoline*)][2-(4-*methyl*-3-*ethylthiazole*)]-γ-*anilomethyltrimethincyanine Iodide*.—This was similarly prepared from the dianilo-compound (3·48 g.) with 2-methyl-Δ^2-thiazoline ethiodide, heating being continued for 7 minutes. Ether precipitated a sticky solid, which hardened on treatment with cold water. It was recrystallised from absolute alcohol (25 c.c.) and thus obtained in 45% yield (Found: I, 25·0. $C_{21}H_{25}N_3IS_2$ requires I, 24·8%). The orange *dye* had m. p. 163° (decomp.). A methyl-alcoholic solution containing pyridine had its absorption maximum at 4170 A., and one containing sulphuric acid at 4265 A. In a chlorobromide emulsion there was very weak sensitisation with the maximum at 5300 A.

[4-(1-*Ethylquinoline*)][2-(3-*ethyl*-Δ^2-*thiazoline*)]-γ-*anilomethyltrimethincyanine Iodide* (X).—3-Ethyl-2-dianilo*iso*propylidenethiazolidine (4·48 g.; 1 mol.), lepidine ethiodide (4·4 g.; 1·1 mols.), and absolute ethyl alcohol (160 c.c.) were mixed together at 0° and kept thus for an hour. The product was filtered off, ground with ether and with water (6·5 g. left), and recrystallised from methyl alchool (120 c.c.), this resulting in an 81% yield (Found: I, 23·4. $C_{26}H_{28}N_3IS$ requires I, 23·45%). The dark green crystals had m. p. 133° (decomp.). A methyl-alcoholic solution containing pyridine had its absorption maximum at 5810 A., whilst one containing sulphuric acid had the maximum at 4950 A. The *dye* conferred very weak extra-sensitivity, extending to 6300 A., and depressed the blue speed.

[2-(3-*Ethyl*-Δ^2-*thiazoline*)][2-(3-*ethylbenzthiazole*)]-α-*anilomethyltrimethincyanine Iodide* (XI.).—This was similarly prepared from the thiazolidine (1·12 g.) with 2-methylbenzthiazole ethiodide in pyridine. After 20 minutes at 0° the dye was filtered off, ground with ether and with water (1·42 g. left), and recrystallised from methyl alcohol (16 c.c.), being obtained in 68% yield (Found: I, 23·05. $C_{24}H_{26}N_3IS_2$ requires I, 23·2%). The crystals were brick-red with a golden reflex and had m. p. 110° (decomp.). The absorption maximum of their methyl-alcoholic solution containing pyridine was at 5100 A., whilst that of one containing sulphuric acid was at 4725 A. The *dye* was photographically inert.

[*Bis*-2-(3-*methyl*-Δ^2-*thiazoline*)]-α-*anilomethyltrimethincyanine Perchlorate*.—This was similarly prepared from 3-methyl-2-dianilo*iso*propylidenethiazolidine (1·60 g.) and 2-methyl-Δ^2-thiazoline methiodide in pyridine. After an hour in ice, precipitation was carried out with ice-cold water. After being washed with water, the solid was extracted with ether (1·61 g. left, 69% yield). The dye iodide was taken up in hot absolute alcohol (20 c.c.) and treated with a hot solution of sodium perchlorate (1·23 g.; 2 mols.) in water (20 c.c.). The yield of washed dye *perchlorate* was 57% (1·27 g.); after recrystallisation from methyl alcohol (100 c.c.) it was 31% and after a second recrystallisation 21% (Found: Cl, 8·15. $C_{19}H_{22}O_4N_3ClS_2$ requires Cl, 8·0%). The orange crystals had m. p. 148° (decomp.) with previous darkening and shrinking. The absorption maximum of their methyl-alcoholic solution containing pyridine was at 4500 A. One containing sulphuric acid had its maximum at 4370 A. The dye sensitised a chloride emulsion weakly to 5000 A., with the maximum at 4400 A.

[2-(3-*Ethyl*-Δ^2-*thiazoline*)][2-(3-*ethylbenzthiazole*)][γβ′-*dimethin*-2′-(3′-*ethyl*-$\Delta^{2'}$-*thiazoline*)]*trimethincyanine Diperchlorate*.—[2-(3-Ethyl-Δ^2-thiazoline)][2-(3-ethylbenzthiazole)]-γ-anilomethyltrimethincyanine iodide (2·60 g.; 1 mol.), 2-methyl-Δ^2-thiazoline ethiodide (2·45 g.; 2 mols.), anhydrous sodium acetate (3·15 g.; 8 mols.), and acetic anhydride (40 c.c.) were heated together at 140—150° for 5 minutes. After cooling, the dye iodide was filtered off, washed (44% yield, 1·49 g.), and recrystallised from methyl alcohol (10 c.c.). The iodide (32% yield; 1 mol.) was dissolved in hot methyl alcohol (6 c.c. per g.) and treated with a hot solution of sodium perchlorate (5 mols.) in water (2 c.c. per c.c. of MeOH). The dye *perchlorate* crystallised (30% yield) and, after recrystallisation from methyl alcohol (110 c.c. per g.), was obtained in 18% yield (Found: Cl, 11·05. $C_{24}H_{31}O_8N_3Cl_2S_2$ requires Cl, 10·8%). The puce powder had m. p. 244° (decomp.). The absorption maximum was at 5045 A. with an inflexion to the curve at 4690 A. The substance slightly depressed the photographic blue speed and sensitised weakly to 5900 A. with the maximum at 5300 A.

[2-(3-*Ethyl*-Δ^2-*thiazoline*)][2-(4-*methyl*-3-*ethylthiazole*][γβ′-*dimethin*-2′-(3′-*ethyl*-$\Delta^{2'}$-*thiazoline*)]*trimethincyanine Diperchlorate*.—[2-(3-Ethyl-Δ^2-thiazoline)][2-(4-methyl-3-ethylthiazole)]-γ-anilomethyltrimethincyanine iodide (1·28 g.; 1 mol.), 2-methyl-Δ^2-thiazoline ethiodide (1·5 mols.), anhydrous sodium acetate (4 mols.), and acetic anhydride (20 c.c.) were heated together at 140—150° for 5 minutes. After precipitation with absolute ether, the product was treated with water. The residue, dissolved in hot spirit, was treated with hot aqueous sodium perchlorate solution and the washed dye *perchlorate*, after recrystallisation from methyl alcohol (30 c.c.), was obtained in 55% yield (0·85 g.) (Found: Cl, 11·3. $C_{21}H_{31}O_8N_3Cl_2S_2$ requires Cl, 11·45%). The maroon crystals had m. p. 220° (decomp.). The absorption maximum was at 5050 A. The sensitising maximum was at 5300 A., sensitisation extending to 5800 A.

[4-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)][γβ′-*dimethin*-2′-(3′-*ethylbenzthiazole*)]*trimethincyanine Di-iodide* (XVII).—[4-(1-Ethylquinoline)][2-(3-ethylbenzthiazole)]-γ-anilomethyltrimethincyanine iodide (VIII) (1·18 g.; 1 mol.), 2-methylbenzthiazole ethiodide (3 mols.), anhydrous sodium acetate (6 mols.), and acetic anhydride (15 c.c.) were heated together at 140—150° for 8 minutes. The product precipitated by absolute ether (40 c.c.) was washed with ether, ground with water, and boiled out six times with methyl alcohol (13 c.c. × 6), the first two fractions of solid being rejected, whilst the last four (0·55 g.; 34% yield) were given a second recrystallisation from methyl alcohol (70 c.c. per g.), resulting in a 19% yield (Found: I, 31·5. $C_{34}H_{33}N_3I_2S_2$ requires I, 31·7%). The bronze *dye* had m. p. 210—212° (decomp.), with previous shrinking, and was a desensitiser. Its absorption maximum was at 6480 A.

[2-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)][γβ′-*dimethin*-2′-(3′-*ethylbenzthiazole*)]*trimethincyanine Di-iodide*.—This was similarly prepared but from [2-(1-ethylquinoline)][2-(3-ethylbenzthiazole)]-γ-anilomethyltrimethincyanine iodide (1·18 g.; 1 mol.), 2-methylbenzthiazole ethiodide (1 mol.), sodium

acetate (4 mols.), and acetic anhydride (8 c.c.) at 140—150° for 2 minutes. The reaction mixture was cooled and filtered, and the solid ground with water (8 c.c.) (1·37 g. obtained). After recrystallisation from methyl alcohol (50 c.c.), the yield was 59% (Found : I, 31·6. $C_{34}H_{33}N_3I_2S_3$ requires I, 31·7%). The bronze crystals had m. p. 228° (decomp.). The absorption maximum was at 6110 A. with an inflexion to the curve at 5700 A. The *dye* desensitised and did not sensitise.

[*Bis*-2-(3-*ethylbenzthiazole*)][αβ′-*dimethin*-2′-(3′-*ethylbenzselenazole*)]*trimethincyanine Di-iodide*.—This was similarly prepared by heating together [bis-2-(3-ethylbenzthiazole)]-α-anilomethyltrimethincyanine iodide (0·60 g.), 2-methylbenzselenazole ethiodide, sodium acetate, and acetic anhydride. The dye was filtered off, washed with ether and with water (4 c.c.) (78% yield, 0·67 g. obtained), and boiled out with, and recrystallised from, methyl alcohol (7 c.c., 100 c.c.), giving a 48% yield (Found : I, 29·8. $C_{32}H_{31}N_3I_2S_2Se$ requires I, 29·7%). The decomposition point of the dark green *dye* lay at about 234° but depended on the rate of heating. The absorption maximum was at 6100 A. with an inflexion to the curve at 5650 A. There was no sensitisation but strong desensitisation.

[2-(3-*Ethyl*-Δ²-*thiazoline*)][2-(3-*ethylbenzthiazole*)][γβ′-*dimethin*-2′-(3′-*ethylbenzthiazole*)]*trimethincyanine Di-iodide*.—This was similarly prepared by 10 minutes' heating of [2-(3-ethyl-Δ²-thiazoline)][2-(3-ethylbenzthiazole)]-γ-anilomethyltrimethincyanine iodide (1·65 g.), 2-methylbenzthiazole ethiodide, sodium acetate, and acetic anhydride. After being washed with ether and with water, the residue (1·39 g.) was recrystallised from methyl alcohol (5 c.c. per g.) and gave a 47% yield (Found : I, 33·55. $C_{28}H_{31}N_3I_2S_3$ requires I, 33·45%). The gold and green crystals had m. p. 211° (decomp.). The absorption maximum was at 5580 A. and the curve had two inflexions on the side of shorter wave-length, one at 5230 and the other at 5355 A. There was weak sensitisation to 6300 A. with the maximum at 5900 A. and depression of blue sensitivity by the *dye*.

[*Bis*-2-(3-*ethyl*-Δ²-*thiazoline*)][αβ′-*dimethin*-2′-(3′-*ethylbenzthiazole*)]*trimethincyanine Diperchlorate* (XVIII).—[2-(3-Ethyl-Δ²-thiazoline)][2-(3-ethylbenzthiazole)]-α-anilomethyltrimethincyanine iodide (XI) (1·82 g.; 1 mol.), 2-methyl-Δ²-thiazoline ethiodide (1·71 g.; 2 mols.), and pyridine (15 c.c.) were heated together at 120° for 3 minutes. Addition of absolute ether precipitated a sticky solid, which was dissolved in hot spirit and treated with a hot aqueous solution of sodium perchlorate (1·9 g.; 4 mols.). The washed *dye* (1·54 g.) was freed from a residue by recrystallisation from methyl alcohol (300 c.c.), and obtained in 49% yield as green crystals with a gold reflex, m. p. 235° (decomp.) (Found : Cl, 10·85. $C_{24}H_{31}O_8N_3Cl_2S_3$ requires Cl, 10·8%). The absorption maximum was at 5580 A., with an inflexion to the curve at 5250 A. It conferred extra-sensitivity to 6200 A. whilst depressing the blue speed.

[4-(1-*Ethylquinoline*)][2-(3-*ethyl*-Δ²-*thiazoline*)][γβ′-*dimethin*-2′-(3′-*ethyl*-Δ²′-*thiazoline*)]*trimethincyanine Diperchlorate*.—[4-(1-Ethylquinoline)][2-(3-ethyl-Δ²-thiazoline)]-γ-anilomethyltrimethincyanine iodide (X), 2-methyl-Δ²-thiazoline ethiodide, anhydrous sodium acetate, and acetic anhydride were boiled together for 5 minutes. The *dye* was precipitated by ether and treated with water. The tar was dissolved in hot spirit and treated with a hot solution of sodium perchlorate in water. The washed solid (1·07 g.; 49% yield) was recrystallised from methyl alcohol (250 c.c.) and thus obtained in 37% yield (Found : Cl, 10·8. $C_{26}H_{33}O_8N_3Cl_2S_2$ requires Cl, 10·9%). The dark green crystals had m. p. 190° (decomp.). The absorption maximum of the unusually broad curve was at 6050 A. with two inflexions on the side of shorter wave-length, one at 5375 A. and one at 5700 A. The dye sensitised very weakly to 6600 A. with a maximum at 6200 A., whilst depressing the blue sensitivity.

(4-(1-*Ethylquinoline*)][2-(3-*ethyl*-Δ²-*thiazoline*)][γβ′-*dimethin*-2′-(3′-*ethylbenzthiazole*)]*trimethincyanine Di-iodide* (XIX).—The intermediate dye (1·35 g.) used in the preceding preparation, 2-methylbenzthiazole ethiodide, and pyridine were boiled together for 2 minutes. The washed solid (0·86 g.) was recrystallised from methyl alcohol (275 c.c.) and thus obtained in 35% yield (Found : I, 33·55. $C_{30}H_{33}N_3I_2S_2$ requires I, 33·7%). The golden crystals had m. p. 242° (decomp.). The absorption maximum was at 6555 A., with an inflexion to the curve at 6150 A. The *dye* showed photographic desensitising power.

[4-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)][γβ′-*dimethin*-2′-(3′-*ethyl*-Δ²′-*thiazoline*)]*trimethincyanine Diperchlorate* (XX).—[2-(3-Ethyl-Δ²-thiazoline)][2-(3-ethylbenzthiazole)]-γ-anilomethyltrimethincyanine iodide (2·36 g.; 1 mol.), lepidine ethiodide (3 mols.), and anhydrous sodium acetate (4 mols.) were ground together and acetic anhydride (24 c.c.) was added. After 70 hours at room temperature, the liquid was filtered off, and the residue, dissolved in hot methyl alcohol (40 c.c.), was added to a hot solution of sodium perchlorate (2·68 g.; 5 mols.) in water (60 c.c.). The washed solid (1·24 g.) was given a second treatment with sodium perchlorate, whereupon the yield was 34% (1·03 g.). It was extracted with hot methyl alcohol (25 c.c.), from which the *dye* crystallised (0·34 g.), and more was obtained (0·27 g.) by further treatment with sodium perchlorate, making a 20% yield (Found : Cl, 10·15. $C_{30}H_{33}O_8N_3Cl_2S_2$ requires Cl, 10·15%). The bronze crystals melted between 145° and 155° (decomp.). The absorption maximum was at 5990 A. Very weak sensitisation extended to 7000 A., with depression of the normal blue sensitivity.

[2-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)][γβ′-*dimethin*-4′-(1′-*ethylquinoline*)]*trimethincyanine Di-iodide*.—[4-(1-Ethylquinoline)][2-(3-ethylbenzthiazole)]-γ-anilomethyltrimethincyanine iodide (VIII) (1·18 g.), quinaldine ethiodide, anhydrous sodium acetate, and acetic anhydride were heated together at 140—150° for 10 minutes. Dye crystallised and more was precipitated by ether. After ether- and water-washing, the product (1·39 g.) was boiled out with, and recrystallised from, methyl alcohol (25 c.c., 140 c.c.), and the yield was 38% (Found : I, 31·75. $C_{36}H_{35}N_3I_2S$ requires I, 31·9%. The brownish-bronze crystalline powder had m. p. 253° (decomp.). The absorption maximum was at 6730 A. with an inflexion to the curve at about 6200 A. The *compound* caused weak photographic sensitisation and strong desensitisation.

It was similarly prepared by use of [2-(1-ethylquinoline)][2-(3-ethylbenzthiazole)]-γ-anilomethyltrimethincyanine iodide and lepidine ethiodide, the yield of recrystallised product being 46% (Found : I, 31·9%).

[2-(1-*Ethylquinoline*)][2-(3-*ethylbenzthiazole*)][γβ′-*dimethin*-2′-(3′-*ethylbenzselenazole*)]*trimethincyanine Di-iodide*.—[(2-(1-Ethylquinoline)][2-(3-ethylbenzthiazole)]-γ-anilomethyltrimethincyanine iodide (1·13 g.), 2-methylbenzselenazole ethiodide, anhydrous sodium acetate, and acetic anhydride were heated together at 73—80° for 10 minutes. The solid was filtered off, washed with ether, and washed

with water until the washings came through blue. The residual dye (1·30 g.; 80% yield) was boiled out with, and recrystallised from, methyl alcohol (5 c.c., 70 c.c.) (44% yield). After a second recrystallisation (104 c.c. per g.), the yield was 28% (Found: I, 30·25. $C_{34}H_{33}N_3I_2SSe$ requires I, 29·9%). The green crystals melted at about 234° (decomp.). The absorption maximum was at 6260 A. with an inflexion to the curve at 5700 A. The *dye* had desensitising power.

When pyridine was used as condensing agent the yields of crude and once recrystallised dye were 61% and 32%, respectively. An alternative preparation from [2-(3-ethylbenzthiazole)][2-(3-ethylbenzselenazole)]-α-anilomethyltrimethincyanine iodide and quinaldine ethiodide in pyridine gave only a 19% yield of crude dye.

Parent Carbocyanines.—[4-(1-*Ethylquinoline*)][2-(4-*methyl*-3-*ethylthiazole*)]*trimethincyanine iodide.* 4-Methyl-2-β-acetanilidovinylthiazole ethiodide (2·07 g.; 1 mol.), lepidine ethiodide (1·5 g.; 1 mol.), triethylamine (1·5 c.c.; 2·2 mols.), and absolute alcohol (45 c.c.) were mixed, and kept in ice for 7 days. The washed *dye* (1·96 g.) was boiled out with, and recrystallised from, methyl alcohol (10 c.c., 50 c.c.), giving a 72% yield (Found: I, 28·3. $C_{20}H_{23}N_2IS$ requires I, 28·2%). The dark blue crystals had m. p. 253° (decomp.), with shrinking from 186°, and sensitised from 5900 to 7100 A. with the maximum at 6750 A. The absorption maximum was at 6295 A.

[2-(1-*Ethylquinoline*)][2-(4-*methyl*-3-*ethylthiazole*)]*trimethincyanine iodide* was similarly prepared, except that quinaldine ethiodide (1·5 g.) replaced lepidine ethiodide. The washed dye (1·3 g.) was boiled out with, and recrystallised from, methyl alcohol (10 c.c., 65 c.c.), giving a 32% yield (Found: I, 28·15. $C_{20}H_{23}N_2IS$ requires I, 28·2%). The green and gold crystals had m. p. 260° (decomp.). The principal absorption maximum was at 5900 A. with a secondary one at 5580 A. Sensitisation extended to 6900 A., with maxima at 5250, 5650, and 6200 A.

[2-(3-*Ethyl*-Δ²-*thiazoline*)][2-(4-*methyl*-3-*ethylthiazole*)]*trimethincyanine iodide* was similarly prepared but from 2-methyl-Δ²-thiazoline ethiodide (1·29 g.). After recrystallisation of the washed dye (0·68 g.) from methyl alcohol (4 c.c.), the yield was 10% (Found: I, 31·15. $C_{14}H_{21}N_2IS_2$ requires I, 31·1%). The maroon crystals had m. p. 213° (decomp.). The absorption maximum was at 4995 A. Sensitisation extended to 5600 with the maximum at 5250 A.

[2-(4-*Methyl*-3-*ethylthiazole*)][2-(3-*ethylbenzthiazole*)]*trimethincyanine iodide* was similarly prepared but from 2-methylbenzthiazole ethiodide (1·53 g.). Recrystallisation of the washed dye (2·25 g.) from methyl alcohol (160 c.c.) gave a 75% yield (Found: I, 27·85. $C_{18}H_{21}N_2IS_2$ requires I, 27·8%). The dark purple crystals had m. p. 252° (decomp.) and sensitised to 6400 A. with maxima at 5220 and 5700 A. The absorption maximum was at 5470 A.

[2-(3-*Ethyl*-Δ²-*thiazoline*)][2-(3-*ethylbenzthiazole*)]*trimethincyanine iodide.* 2-β-Acetanilidovinyl-Δ²-thiazoline ethiodide (4·02 g.; 1 mol.), 2-methylbenzthiazole ethiodide (1 mol.), triethylamine (1 mol.), and absolute alcohol (50 c.c.) were mixed, and kept in ice for 7 days. The washed solid (2·85 g.) was boiled out with, and recrystallised from, methyl alcohol (10 c.c., 40 c.c.), and gave a 32% yield. After two more recrystallisations (21 c.c. per g.), the yield was 22% (Found: I, 28·65. $C_{17}H_{21}N_2IS_2$ requires I, 28·55%). The orange-red *dye* had m. p. 237° (decomp.). The absorption maximum was at 5020 A. and the sensitising maximum at 5300 A., sensitisation extending to 5700 A.

[4-(1-*Ethylquinoline*)][2-(3-*ethyl*-Δ²-*thiazoline*)]*trimethincyanine iodide* was similarly prepared but with lepidine ethiodide (2·99 g.) replacing 2-methylbenzthiazole ethiodide, and with excess of triethylamine (2·2 mols.). Recrystallisation of the washed dye (3·9 g.) from methyl alcohol (100 c.c.) gave a 72% yield (Found: I, 29·1. $C_{19}H_{23}N_2IS$ requires I, 28·15%). The dark violet iridescent crystals had m. p. 228° (decomp.) and sensitised from 5000 to 6400 A. with the maximum at 6050 A. and a minimum at 5000 A. The absorption maximum was at 5765 A.

[2-(4-*Methyl*-3-*ethylthiazole*)][2-(3-*ethylbenzselenazole*)]*trimethincyanine iodide.* 2-β-Acetanilidovinylbenzselenazole ethiodide (4·97 g.; 1 mol.), 2 : 4-dimethylthiazole ethiodide (1 mol.), anhydrous potassium carbonate (180-mesh; 1·2 mols.), and absolute alcohol (20 c.c.) were mixed, and kept in ice for some days. The washed solid (4·24 g.) was boiled out with, and recrystallised from, methyl alcohol (50 c.c., 200 c.c.) and gave a 39% yield (Found: I, 25·1. $C_{18}H_{21}N_2ISSe$ requires I, 25·2%). The dark violet-blue *dye* had m. p. 257° (decomp.) and sensitised uniformly from 5000 to 6000 A., sensitisation extending to 6400 A. The absorption maximum was at 5510 A.

[2-(1 : 3 : 3-*Trimethylindolenine*)][2-(3-*ethylbenzthiazole*)]*trimethincyanine iodide.* 2-β-Acetanilidovinylbenzthiazole ethiodide (2·5 g.; 1 mol.), 2 : 3 : 3-trimethylindolenine methiodide (1 mol.), anhydrous sodium acetate (0·5 g.), and acetic anhydride (15 c.c.) were boiled together for 15 minutes (I.C.I. Ltd., Piggott, and Rodd, B.P. 354,898/1930). The washed solid (1·58 g.) was boiled out with methyl alcohol (10 c.c.), which extract gave a 40% yield of dark steel-blue crystals, m. p. at about 185—188° with shrinking from 158° (Found: I, 26·15. $C_{23}H_{25}N_2IS$ requires I, 26·0%). The *dye* had its absorption maximum at 5430 A. and sensitised to 6400 A. with maxima at 5400 and 5950 A.

[2-(1 : 3 : 3-*Trimethylindolenine*)][2-(3-*ethylbenzselenazole*)]*trimethincyanine perchlorate.* 3-Ethyl-2-aniloethylidenebenzselenazoline (1·64 g.; 1 mol.), 2 : 3 : 3-trimethylindolenine methiodide (1 mol.), anhydrous sodium acetate (8 mols.), and acetic anhydride (30 c.c.) were boiled together for 3 minutes. The reaction mixture was treated hot with a solution of sodium perchlorate (4 mols.) in water (150 c.c.). The resultant dye *perchlorate* (2·9 g.), after recrystallisation from methyl alcohol (75 c.c.), was obtained in 82% yield (Found: Cl, 7·05. $C_{23}H_{25}O_4N_2ClSe$ requires Cl, 7·0%). The bluish-grey, metallic-looking crystals had m. p. 170° (decomp.) and depressed blue sensitivity but gave extra-sensitisation to beyond 6100 A., with the maximum at 5750 A. The narrow absorption curve had its maximum at 5500 A.

We thank our colleagues for data supplied: Miss M. D. Gauntlett for absorption curves, Dr. B. H. Carroll, Dr. E. B. Knott, and Mr. J. Morgan for sensitising tests, and Mr. V. E. Lead for pH measurements. We are especially indebted to Dr. J. T. Hewitt, F.R.S., and to Dr. A. D. Mitchell for their helpful consideration of the nomenclature.

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376. *Diterpenes. Part I. The Identity of Kaurene with Podocarprene.*

By Lindsay H. Briggs and R. W. Cawley.

The diterpenes kaurene, from *Agathis australis*, and podocarprene, from *Podocarpus* spp., are shown to be identical.

From the highest-boiling fraction of the essential oil of *Agathis australis* ("kauri"), Hosking (*Rec. Trav. chim.*, 1928, **47**, 578; 1930, **49**, 1036) isolated a crystalline diterpene, kaurene, $C_{20}H_{32}$, forming a monohydrochloride from which the hydrocarbon could be recovered unchanged, a dihydro-derivative by catalytic hydrogenation, and pimanthrene on dehydrogenation. Kaurene and its derivatives were all optically inactive. It has already been pointed out in a review of the diterpenes (Briggs, *Proc. Aust. New Zealand Assoc. Adv. Sci.*, 1937, **23**, 45) that the melting points of kaurene and its derivatives approximate to those of α-podocarprene from the essential oils of *Podocarpus macrophylla* (Nishida and Uota, *Bull. Agric. Chem. Soc. Japan*, 1930, **7**, 1—3) and *Sciadopitys verticillata* (Kawamura, *Bull. Imp. Forestry Exp. Sta. Tokyo*, 1931, No. 31, 93) but that further work would be necessary to make a full comparison (the reference to "isokaurene" in this review is an error). With the kind permission of the late Dr. J. R. Hosking we have continued the investigation on kaurene.

By distilling the essential oil of *Agathis australis* at a lower pressure than that used by Hosking and omitting all distillations from sodium we have obtained an optically active diterpene, the properties of which and of its derivatives leave no doubt as to its identity with α-podocarprene, which also does not depress its melting point. In the following comparison the data in brackets refer to those of α-podocarprene: hydrocarbon, m. p. 50° (50—50·5°), $[\alpha]_D^{20°}$ −75·2° (−71·9°); hydrochloride, m. p. 114—115° (115—117°), $[\alpha]_D^{20°}$ −40·0° (−27·4°); hydrocarbon recovered from the hydrochloride, m. p. 64° (65°), $[\alpha]_D^{20°}$ −25·9° (−27·1°); dihydro-derivative, m. p. 88° (86—87°), $[\alpha]_D^{20°}$ −35·7° (−29·3°); nitrosochloride, m. p. 138°, decomp. (136°, decomp.*); nitrosate, m. p. 135°, decomp. (140°, decomp.). The optical inactivity of Hosking's kaurene is, in our opinion, probably due to heat- or alkali-isomerisation. There is no need to retain separate names for the optically active and inactive forms, and we suggest retaining only the name kaurene for this hydrocarbon.

Nishida and Uota (*loc. cit.*; *J. Agric. Chem. Soc. Japan*, 1931, **7**, 157, 954) have described the original crystalline podocarprene (designated α-), m. p. 50°, and two other isomers, β-podocarprene, the high-boiling liquid diterpene from the oil, and γ-podocarprene, m. p. 197—199°, a hydrocarbon obtained by the action of alcoholic potash on the hydrochloride which both α- and β-podocarprene give with hydrogen chloride. Kawamura (*loc. cit.*), on the other hand, obtained another isomer, δ-podocarprene, m. p. 65°, naturally occurring along with α-podocarprene and identical with the product obtained by the action of alcoholic potassium acetate on the hydrochloride of α-podocarprene. α- and δ-Podocarprenes afforded the same hydrochloride and dihydro-derivative, suggesting that the difference between these isomers is in the position of the double bond.

We have confirmed Kawamura's results, and since the change from α- to δ-podocarprene is similar to that of phyllocladene to *iso*phyllocladene, we suggest naming the isomers, m. p. 50° and 65°, kaurene and *iso*kaurene respectively. Constitutional work on these compounds is in progress.

Experimental.

371 Lb. of leaves and terminal branchlets of *Agathis australis*, collected in the Waitakere Ranges near Auckland, produced on steam-distillation 258 g. (0·26%) of light yellow oil. This was distilled in a Bower and Cooke type of column (*Ind. Eng. Chem. Anal.*, 1943, **15**, 290) at 20 mm. pressure for the major part of the oil, and at 5 mm. in the final stages, the bath temperature not exceeding 215°, until the sesquiterpene fractions were mostly removed. The residual oil (54 g.) was removed with ether and distilled at 0·01 mm. in a modified Craig column (*ibid.*, 1937, **9**, 441), 20 cm. long, without condenser, with a side arm dipping into a series of receivers, the results being recorded in the following table.

Fraction no.	B. p./0·01 mm.	$d_4^{25°}$.	$n_D^{25°}$.	$[R_L]_D$.	$[\alpha]_D^{25°}$.	Wt., g.
I	115°	—	1·5189	—		0·8
II	120—130	—	1·5210	—		6·7
III	130	—	1·5216	—		7·8
IV	130	0·9890	1·5225	84·0°	−26·2°	12·5
V	130—140	0·9906	1·5230	83·9	−35·1	10·1
VI	130—140	0·9950	1·5229	83·5	−29·5	5·45

* The m. p. is incorrectly recorded as 163° in the abstract (*Brit. Abs.*, 1933, *B*, 321) and in the review by one of us (L. H. B.).

Although fractions IV and VI solidified on cooling to −15° and seeding, it was subsequently found better to dissolve the fractions in warm absolute alcohol, allow them to cool slowly, and seed them with a crystal of podocarprene. The diterpene then crystallised in long radiating needles and after repeated crystallisation from the same solvent had $[\alpha]_D^{20°}$ −75·1° ($l = 1$; c, 4·0 in chloroform) and m. p. 50°, undepressed by authentic podocarprene, kindly forwarded by Professor Nishida. The yield of pure material was only 3·1 g., 1·2% of the original essential oil. The liquid diterpene residues have not yet been investigated.

Kaurene Hydrochloride.—1·5 G. of fraction IV were dissolved in a mixture of glacial acetic acid (2 c.c.) and dry ether (0·5 c.c.), the solution cooled in ice, and dry hydrogen chloride passed over the liquid. The crystalline product (1·05 g.) after repeated crystallisation from ethyl acetate formed long colourless needles, m. p. 114—115°, $[\alpha]_D^{20°}$ −40·0° ($l = 1$; c, 3·1 in chloroform). Pure kaurene gave the same product in higher yield.

iso*Kaurene.*—A solution of kaurene hydrochloride (500 mg.) in alcohol (10 c.c.) was boiled under reflux with potassium hydroxide (300 mg.) for 6 hours. The crystalline precipitate, formed in quantitative yield on pouring the solution into water (100 c.c.), after repeated crystallisation from absolute alcohol gave irregular colourless plates, m. p. 64°, $[\alpha]_D^{20°}$ −25·9° ($l = 1$; c, 0·35 in chloroform). *iso*Kaurene formed kaurene hydrochloride, identical with this (m. p. and mixed m. p.), when treated with hydrogen chloride.

Dihydrokaurene.—Kaurene (100 mg.) in glacial acetic acid (10 c.c.) was hydrogenated at 2 atm. pressure with palladised charcoal (100 mg.). The product crystallised on concentration of the filtered solution and after further recrystallisations from the same solvent formed long colourless needles, m. p. 88°, $[\alpha]_D^{20°}$ −35·7° ($l = 1$; c, 0·33 in chloroform). On the small scale employed no isomeric hydrocarbon [cf. the preparation of α- and β-dihydrophyllocladene (Briggs, *J.*, 1937, 79; Brandt, *New Zealand J. Sci. Tech.*, 1938, **20**, 8B)] could be isolated from the mother-liquors.

Kaurene Nitrosochloride.—Kaurene (200 mg.) and amyl nitrite (170 mg.) were dissolved in dry ether (0·3 c.c.), cooled to −12°, and a mixture of concentrated hydrochloric acid (0·13 c.c.) and ether (0·2 c.c.) added dropwise. After standing, the nitrosochloride was precipitated from the solution by the addition of absolute alcohol, and purified by solution in chloroform and precipitation with absolute alcohol, and then had m. p. 138° (decomp.).

Kaurene Nitrosate.—Kaurene (200 mg.) and amyl nitrite (170 mg.) were dissolved in dry ether (0·2 c.c.), cooled to −11°, and a mixture of concentrated nitric acid (0·16 c.c.) in dry ether (0·2 c.c.) added dropwise. The product was isolated and purified as for the nitrosochloride and then had m. p. 135°. The yields in both cases were low.

We are indebted to the Chemical Society and the Royal Society of New Zealand for grants.

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377. *Sophora Alkaloids. Part V. The Alkaloids of the Seeds of a Possibly New Species from Anawhata, New Zealand.*

By LINDSAY H. BRIGGS and J. L. MANGAN.

From the seeds of a possibly new species, cytisine, methylcytisine, and matrine have been isolated. The bearing of these results on the botanical classification is discussed.

DR. H. H. ALLAN, Director of the Botany Division, Department of Scientific and Industrial Research, New Zealand, has suggested to the authors that the tree of which the examination is now reported and which occurs in a restricted area round Anawhata, near Auckland, is either a variety of *S. microphylla*, already examined (Part I, *J.*, 1937, 1795), or a distinct species. Baker and Smith (" A Research on the Eucalypts and their Essential Oils ", 1920, 2nd Edtn.) and Manske (*Canadian J. Res.*, 1939, **17**, *B*, 1) have shown that species of *Eucalyptus* and *Senecio* respectively, taxonomically indistinguishable, can be separated by differences in the essential oils and the alkaloids they contain, and it was considered, therefore, that an examination would be of assistance in its botanical classification as attempted in Part IV (*J.*, 1942, 555).

Following the methods outlined in earlier papers of this series, extraction of the seeds has yielded a crude alkaloid mixture from which cytisine, methylcytisine, and matrine have been identified. Only 55% of the alkaloids present in the crude mixture distilled in a high vacuum, of which 81% was accounted for by the isolation, as either the free base or the picrate, of methylcytisine (71%), cytisine (7%), and matrine (3%), corresponding to 40, 4, and 1·5% respectively of the total alkaloids, and no crystalline material could be obtained from the distillation residues. In an attempt to obtain a better quantitative yield of the alkaloids present, aliquot portions of the crude alkaloid mixture were converted into their picrates and picrolonates severally and fractionally crystallised. No sharp separation could be achieved with the picrates, from which only those of cytisine and methylcytisine were obtained. Crystallisation of the picrolonates, however, afforded a better separation in amounts

corresponding to 23 and 29% of cytisine and methylcytisine, respectively, but from neither method could derivatives of matrine be isolated. No other bases, *e.g.*, sophochrysine, could be detected by any of the above methods.

In this series of experiments on the alkaloids of the seeds of *S. tetraptera*, *S. microphylla*, and this tree, although the total yield of alkaloids actually isolated in a pure state is far from quantitative, the methods of isolation have been similar in all cases and may therefore be considered roughly comparable. The composition (in %) of the alkaloids is given in the following table:

Species.	Matrine.	Methylcytisine.	Cytisine.	Sophochrysine.
S. tetraptera	45	3	—	1
S. microphylla	27	20	0·05	trace
Unknown *Senecio* spp.	1·5	40	4 *	—

* Isolated by solvent extraction; 23% through separation of the picrolonates.

There is thus a marked difference between the composition of the alkaloids of *S. microphylla* and this tree, as much as the difference between that of *S. microphylla* and *S. tetraptera*. If phytochemical evidence is to be taken into account in the differentiation of species, then the above results would support the classification of this plant as a new species.

Burger (*J. Amer. Chem. Soc.*, 1945, **67**, 1615) has recommended the use of lithium hydroxide for regenerating bases from their picrates owing to the greater solubility of lithium picrate than of sodium or potassium picrate. A similar solubility relationship holds for the lithium, sodium, and potassium picrolonates and we have shown that the free bases are also conveniently regenerated from their picrolonates by using lithium hydroxide.

Experimental.

The obvious differences of this species or variety are that the leaves consist of about 40 pairs of pinnæ, *ca.* 4 mm. long, much smaller than those of *S. microphylla*, and the characteristic dull greyish-green foliage in contrast to the normal bright green of *S. microphylla*.

1·9 Kg. of the crushed seeds of this species gathered from an area at Anawhata less than 50 yards across were worked up as described in Part II (*J.*, 1938, 1206). Chloroform is twice as efficient as trichloroethylene or ether in removing the alkaloids from the aqueous solution, but even then continuous extraction for 150 hours was required. The crude alkaloid mixture was obtained as a brown viscous oil (40 g.). An aliquot sample was dissolved in 1% hydrochloric acid and filtered. After the addition of excess of silicotungstic acid the granular precipitate was filtered off, dried at 110°, and ignited to red heat. Assuming the composition of the precipitate to be $SiO_2,12WoO_3,2H_2O,x$(alkaloid), converted on ignition into $SiO_2,12WoO_3$, the percentage of alkaloid in the crude mixture was found to be 69·5% and the total yield of alkaloids from the seeds *ca.* 1·5%.

Separation of Bases.—(a) *By distillation and solvent extraction.* No apparent separation occurred during the distillation of the crude bases, a single fraction being obtained, b. p. 165—190°/0·01—0·02 mm., with the final bath temperature 240°. Of 19·5 g. distilled, 5·8 g. were lost as solvent, corresponding almost exactly to the figure indicated by the silicotungstate method (it is extremely difficult to remove solvent from this mixture except by distillation). Of the residue, 7·6 g. (55% of the total alkaloids) distilled, leaving a residue of 6·1 g. (45% of the total alkaloids). The distilled bases rapidly crystallised in contact with light petroleum (b. p. below 40°) but separation was best achieved by extraction in a Soxhlet extractor. The material was first exhaustively extracted with this solvent, and repeated crystallisation of the material separating on cooling gave 4·38 g. of base A, m. p. 128—131°. From the mother-liquors 0·21 g. of base B was obtained in crystalline condition, m. p. 66—72°, also from the same solvent. The intermediate fractions consisted of 1·29 g. of oily base A and 0·66 g. of oily base B, but only from the former could a further quantity of base A be obtained as the picrate (1·24 g.).

The residue in the Soxhlet readily and completely dissolved in chloroform (cf. sophochrysine, which is only sparingly soluble in chloroform). The semisolid material remaining after removal of the chloroform by crystallisation from benzene–light petroleum (b. p. 100—120°) and again from benzene yielded base C, m. p. 155·5—157° (0·24 g.). The mother-liquors afforded a further quantity (0·64 g.) as the picrate. From these quantities the yields of bases A, B, and C were calculated to be 71, 2·8, and 7%, respectively, of the distilled bases, or 40, 1·5, and 4%, respectively, of the total alkaloids.

No other bases could be isolated from the mother-liquors, nor could any crystalline material be obtained from the residue of the distillation.

Base A. The m. p. of this base, identified as methylcytisine, was raised to a constant value of 135—136° by recrystallisation from light petroleum (b. p. under 40°), and from this material the picrate, m. p. 224°, and picrolonate, m. p. 223°, were prepared (for the literature on all these bases and derivatives, see Parts I—IV). No depressions of m. p. were observed on admixture with methylcytisine and its appropriate derivatives respectively; $[\alpha]_D^{18°}$ −194·1° (*l* = 0·25; *c*, 2·025 in water).

Base B. Recrystallisation of this base, identified as α-matrine, from light petroleum (b. p. below 40°) afforded long colourless needles, m. p. 76—77°, from which the picrate, m. p. 60—135°, and aurichloride, m. p. 199—200° (decomp.), were prepared. The m. p.s of the free base and its aurichloride were not depressed by authentic specimens, and the readily prepared picrate shows the indefinite m. p. characteristic also of matrine picrate; $[\alpha]_D^{18°}$ +42·3° (*l* = 0·25; *c*, 1·700 in water).

Base C. This has been identified as cytisine, the purified base separating from absolute alcohol–acetone or amyl alcohol in colourless needles, m. p. 156—157°; $[\alpha]_D^{15°}$ −126·2° (l = 0·25; c, 1·965 in water).

The free base, its aurichloride, m. p. 221°, picrolonate, m. p. 266° (decomp.), and its benzenesulphonyl derivative, m. p. 259° (Ing, *J.*, 1935, 1053, records m. p. 263—264°), were not depressed in m. p. by cytisine and its appropriate derivatives respectively.

(b) *By fractional crystallisation of the picrolonates.* 0·5510 G. of the crude bases was dissolved in a little water, filtered, and to the hot solution picrolonic acid (0·6 g.) in alcohol was added. Systematic crystallisation of the crude picrolonates formed and working up of the mother-liquors therefrom afforded only two products: (*a*) golden needles, m. p. 269° (decomp.), from 50% alcohol, and (*b*) short yellow needles, m. p. 224°, from 50% methyl alcohol and absolute alcohol, undepressed in m. p. by cytisine and methylcytisine picrolonates, respectively. The yields of these derivatives corresponded to 23% and 29% of the total alkaloids, respectively.

Cytisine picrolonate (75 mg.) was decomposed with lithium hydroxide solution, and the free base extracted with chloroform and converted into the perchlorate. After recrystallisation from methyl alcohol it formed colourless needles, m. p. and mixed m. p. 296° (decomp.).

(c) *By fractional crystallisation of the picrates.* 0·5016 G. of the crude bases was dissolved in water, and picric acid (1 g.) in hot water added. Careful fractionation of the product and working up of the mother-liquors again afforded only two products: (*a*) yellow needles from water, m. p. 228·5—229°, and (*b*) yellow needles from aqueous alcohol, m. p. above 300°. The former was not depressed in m. p. by methylcytisine picrate. The latter corresponds to the m. p. of 302° recorded by Manske (*Canadian J. Res.*, 1943, **21**, *B*, 144) for cytisine picrate, which is considerably higher than the values 270° and 278° recorded by Clemo and Raper (*J.*, 1935, 10) and by Briggs and Ricketts (Part I, *loc. cit.*), respectively. The identity with cytisine, however, was confirmed by conversion of the picrate into the free base by Burger's method and conversion into the picrolonate. After recrystallisation from aqueous alcohol this formed yellow needles, m. p. and mixed m. p. 269° (decomp.) (Found: C, 55·4; H, 4·7. Calc. for $C_{11}H_{14}ON_2$,$C_{10}H_8O_8N_4$: C, 55·5; H, 4·85%).

Despite the indefinite m. p. of matrine picrate, it crystallises readily and would have been observed in the above separation if present in quantity.

The analysis is by Mr. J. Mills, University of Adelaide.

We are indebted to the Chemical Society and the Australian and New Zealand Association for the Advancement of Science for continued grants.

AUCKLAND UNIVERSITY COLLEGE, AUCKLAND, NEW ZEALAND. [*Received, December* 31*st*, 1947.]

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378. *Alkaloids of New Zealand* Senecio *Species. Part I. The Alkaloid from* Senecio kirkii.

By LINDSAY H. BRIGGS, J. L. MANGAN, and W. E. RUSSELL.

A new alkaloid, *senkirkine*, $C_{18}H_{25}O_6N$, has been isolated from the bark and leaves of *Senecio kirkii*. Hydrolysis affords senecic acid lactone and an oily necine, probably $C_8H_{13}O_3N$, isolated as an amorphous picrate and aurichloride.

THE genus *Senecio*, the largest in the *Compositæ* or flowering plants, contains over a thousand species, and of the individual species examined a large number have been found to contain alkaloids (for a review, see Manske, *Ann. Rev. Biochem.*, 1944, 533). New Zealand has 30 species, all endemic except one, *S. lautus*, which extends to Australia. So far none of the New Zealand species has been examined although the introduced species, *S. jacobæa* ("ragwort"), which has spread over wide areas of New Zealand causing "Winton disease" in horses and cattle (Gilruth, *Rep. New Zealand Dept. Agric.*, 1903, 228), has been examined by Hosking and Brandt (*New Zealand J. Sci. Tech.*, 1936, **17**, 638; cf. also Manske, *Canadian J. Res.*, 1931, **5**, 651, and Barger and Blackie, *J.*, 1937, 584).

S. kirkii, a shrub 6—12 feet high and often epiphytic on other trees, is common over the North Island of New Zealand. From both the leaves and the stem bark there has been isolated by the normal procedure, a new alkaloid, $C_{18}H_{25}O_6N$, isomeric with jacobine and retrorsine, for which the name *senkirkine* is proposed. Hydrolysis of the base with baryta affords senecic acid lactone, $C_{10}H_{14}O_4$, as the necic acid, and an oily necine, from which only an amorphous picrate and aurichloride were prepared but not analysed. If we assume normal hydrolysis, $C_{18}H_{25}O_6N_4 + H_2O \longrightarrow C_{10}H_{14}O_4 + C_8H_{13}O_3N$, then the necine would have the formula $C_8H_{13}O_3N$, and be thus identical or isomeric with isatinecine from *S. isatideus* and *S. retrorsus* (de Waal, *Onderstepoort J. Vet. Sci. Animal Ind.*, 1939, **12**, 155; 1940, **14**, 433) but no details or derivatives are recorded in the abstracts of these papers.

EXPERIMENTAL.

2·8 Kg. of the dried bark from trees at Anawhata, near Auckland, collected just before the flowering period, were extracted exhaustively (180 hours) with alcohol in a Soxhlet-type extractor until free from

alkaloid. Most of the alcohol was distilled off from the extract, the final fraction by steam-distillation, which also removed a quantity (0·4%) of volatile oil. The aqueous residue was acidified with acetic acid and decanted from a large amount (30%) of resin. The resin, even after being washed, contained appreciable amounts of alkaloid, which was removed by taking up the resin in ether and extracting it with dilute acetic and finally dilute hydrochloric acid. The combined acid solutions were extracted with chloroform, made alkaline with ammonia, and exhausted of alkaloid with chloroform. The chloroform solution was extracted with 2% acetic acid solution, giving an almost colourless extract. This was again basified with ammonia and yielded to chloroform, after drying, a brown, very viscous oil which partly crystallised on standing. Recrystallisation from acetone or preferably ethyl acetate formed large plates of constant m. p. 197—198° (Found: C, 62·4, 62·5, 62·6; H, 7·4, 7·4, 7·2; N, 4·1. $C_{18}H_{25}O_6N$ requires C, 61·6; H, 7·1; N, 4·0%); $[\alpha]_D^{15°}$ −6·2° (l = 0·25; c, 1·91 in chloroform).

The residue from which the crystalline alkaloid had separated was converted into the solid picrate, which was repeatedly purified, and the free base regenerated with lithium hydroxide by Burger's method (*J. Amer. Chem. Soc.*, 1945, **67**, 1615). Only the above base was isolated, and there was no evidence for the presence of other bases. The total yield from both processes was 550 mg., or 0·02% of the dry bark. By a similar procedure *senkirkine* was isolated from the leaves.

The *picrate*, formed from the base (22 mg.) and picric acid (70 mg.) in aqueous solution, recrystallised from water in elongated plates, m. p. 225·5—226° (Found: C, 51·2; H, 4·9; N, 9·7. $C_{18}H_{25}O_6N,C_6H_3O_7N_3$ requires C, 49·7; H, 4·9; N, 9·7%). The *picrolonate*, formed by the addition of picrolonic acid (16 mg.) in alcohol to the base (20 mg.) in water, recrystallised from 50% alcohol in clustered needles, m. p. 109—110° (shrinking at 106°) (Found: C, 54·1; H, 6·1; N, 12·2. $C_{18}H_{25}O_6N,C_{10}H_8O_5N_4$ requires C, 54·6; H, 5·4; N, 11·4%).

Hydrolysis of Senkirkine.—A solution of the base (520 mg.) in 2N-baryta (10 c.c.) was gently boiled under reflux for one hour (whereupon rapid darkening occurred), cooled, saturated with carbon dioxide, and the barium carbonate filtered off. The solution was acidified to Congo-red with hydrochloric acid and exhaustively extracted with ether in a continuous apparatus. After drying and removal of the ether, the residual, partly solid oil was repeatedly crystallised from ethyl acetate, forming long colourless needles, m. p. 157—158°, yield 50 mg. (Found: C, 60·8; H, 7·0. Calc. for $C_{10}H_{14}O_4$: C, 60·6; H, 7·1%). Direct titration (with phenolphthalein as indicator) showed it to be a monobasic acid (equiv., 203. Calc. for $C_{10}H_{14}O_4$: equiv., 198), but by the further action of sodium hydroxide solution at 100° followed by back titration with acid the presence of a second potential acid, *e.g.*, lactone group, was indicated. The acid solution on evaporation furnished the original compound. The formula, m. p. [Richardson and Warren (*J.*, 1943, 452) record m. p. 156° (corr.)], crystalline shape, solubilities, and chemical properties all agree with those of senecic acid lactone, with which we consider it is identical.

The Necine.—The aqueous solution from the hydrolysis, which gave copious precipitates with alkaloidal reagents, was evaporated to a small volume in a desiccator. An aliquot portion was converted into the picrate, which could not be crystallised from alcohol, acetone, or aqueous alcohol but separated from hot water as an amorphous solid, m. p. 175—180° (decomp.). The free base was regenerated from the purified picrate by Burger's method but separated only as an oil, very soluble in water and extracted therefrom only with difficulty by chloroform. On addition of auric chloride solution to another aliquot portion of the necine, an aurichloride separated in amorphous form (decomp. 165—166°), which, however, could not be crystallised.

The analyses are by Drs. Weiler and Strauss, Oxford, and Mr. J. Mills, University of Adelaide.

We express our thanks to the Chemical Society and the Australian and New Zealand Association for the Advancement of Science for continued grants.

AUCKLAND UNIVERSITY COLLEGE, AUCKLAND, NEW ZEALAND. [*Received, December 31st*, 1947.]

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379. *Monothioethylene Glycol and Thiodiglycol.*

By F. N. WOODWARD.

Gaseous ethylene oxide (2 mols.) and hydrogen sulphide (1 mol.) react in stirred preformed thiodiglycol (I) at 45—60° to give (I) in quantitative yield. Excess of hydrogen sulphide results in formation of (I) and monothioethylene glycol (II) in the ratio 2 : 3.

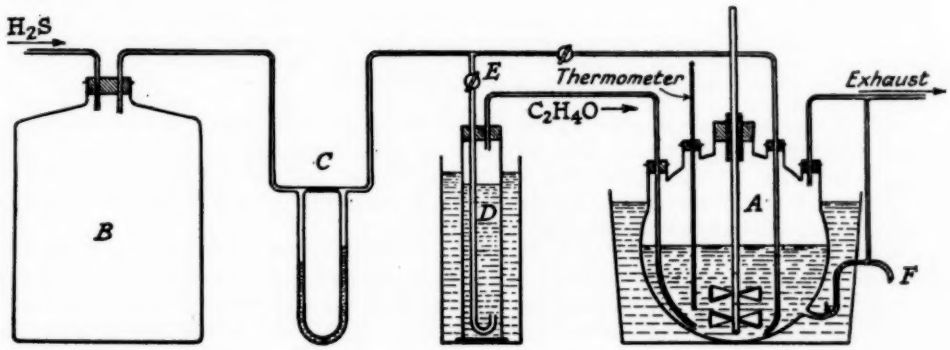
BEFORE 1932, 2 : 2′-dihydroxydiethyl sulphide (thiodiglycol) (I) was only obtainable by the interaction of ethylene chlorohydrin and sodium sulphide (Gomberg, *J. Amer. Chem. Soc.*, 1919, **41**, 1414), and 2-hydroxyethanethiol (monothioethylene glycol) (II) only from ethylene chlorohydrin and sodium hydrogen sulphide (Carius, *Annalen*, 1862, **124**, 257). Bennett (*J.*, 1921, **119**, 422; 1922, **121**, 2146) improved the latter method and obtained the pure thiol in 50—55% yield and studied its properties in detail. In the course of many preparations of (II) by Bennett's method we have only obtained 25—30% yields and we have been unable to obtain it by the reduction of 2 : 2′-dihydroxydiethyl disulphide as described by Fromm and Jorg (*Ber.*, 1925, **58**, 304).

The possibility of preparing (I) and (II) by the interaction of ethylene oxide and hydrogen sulphide was first suggested and investigated in these laboratories in 1932, but at the request of the War Office, under whose ægis the investigation was carried out, the results were not then published. The lifting of this restriction now permits us to record these early findings.

The first method developed allowed equimolecular amounts of ethylene oxide and alcoholic sodium hydrogen sulphide to react in the presence of excess of hydrogen sulphide, whereby on acidification of the reaction product a mixture of (I) and (II) in 24% and 30% yields respectively was obtained according to the scheme

$$\underset{\text{(II.)}}{2HO\cdot C_2H_4\cdot SH} \xleftarrow{2C_2H_4O} 2NaSH \rightleftharpoons H_2S + Na_2S \xrightarrow{2C_2H_4O} \underset{\text{(I.)}}{S(C_2H_4\cdot OH)_2}$$

Subsequently it was found preferable to allow the gaseous reactants to mix in briskly stirred preformed (I) at 45—60°; 2 mols. of the oxide and 1 mol. of the sulphide then yielded pure (I) almost quantitatively, whilst with excess hydrogen sulphide 60% yields of (II) and 40% of (I) were obtained under the best conditions.



Interaction of (II) and ethylene chlorohydrin in the presence of anhydrous sodium carbonate afforded (I) in 50% yield.

Since 1932, several variations of the method have been described independently. Tschitschibabin (F.P. 704,216, August 1934) proposed the use of water, certain lower alcohols, alumina, and activated charcoal as catalysts, and Nenitzescu and Scarlatescu (*Ber.*, 1935, **68**, 587; *Antigaz*, Bucharest, 1935, Oct. 9th, p. 12; Dec. 11th, p. 3) claimed a high yield of (I) by passing a mixture of ethylene oxide and hydrogen sulphide up a column packed with rings moistened with (I); Tseou and Pan (*J. Chinese Chem. Soc.*, 1939, **7**, 29) used a similar method, whilst Othmer and Kein (*Ind. Eng. Chem.*, 1940, **32**, 160) studied the kinetics of the reaction.

Experimental.

Ethylene Oxide and Sodium Hydrogen Sulphide.—A solution of sodium (23 g.) in rectified spirits (400 c.c.) was saturated with hydrogen sulphide (6 hours). Ethylene oxide (44 g.) and hydrogen sulphide were then bubbled through the mixture during one hour, the temperature being kept below 30° throughout. After standing overnight, the reaction mixture was poured into water, the solution neutralised by the addition of glacial acetic acid (60 c.c.), and finally extracted with ether. The ethereal extract was dried (Na_2SO_4), the solvent removed, and the residue distilled. A lower fraction (24 g.) was obtained, b. p. 58°/12 mm., identified as 2-hydroxyethanethiol through its bis-α-naphthylurethane, m. p. 173°, and a higher fraction (29 g.) b. p. 147°/6 mm., which afforded a *bis-α-naphthylurethane*, m. p. 143°, identical with that obtained from an authentic sample of (I) (Found: S, 7·09. $C_{26}H_{12}O_4N_2S$ required S, 7·15%).

Ethylene Oxide and Hydrogen Sulphide.—Hydrogen sulphide and vapourised ethylene oxide were introduced separately into the five-necked litre flask *A* (see Fig.) through tubes dipping beneath the surface of 100 c.c. of (I). The mixture was agitated by a stirrer at 1900 r.p.m. and a reaction temperature of 50—60° was maintained. The hydrogen sulphide, after being scrubbed through aqueous sodium hydrogen sulphide to remove hydrochloric acid, was allowed to pass through the compensating vessel *B* at 40—45 l./hr., as measured on the flow-meter *C*, whilst the ethylene oxide was evaporated in a measuring cylinder *D* immersed in a water-bath at 15—20°, uniform evaporation being ensured by means of a small hydrogen sulphide leak through the side tube *E*. The ethylene oxide input rate, measured by noting the rate of diminution in volume of the liquid in *D*, was maintained at 0·5 c.c./min., corresponding to 200% excess of hydrogen sulphide. The reaction product contained (I) and (II) (44%) only, the overall efficiency of conversion of ethylene oxide being about 90%. The thiol (II) obtained by distillation (b. p. 96—97°/100 mm.) from the reaction product had the following characteristics: b. p. 53·5°/10 mm., 68°/20 mm., 77°/37mm., 78·5°/40 mm., 92°/78 mm., 98/100 mm., 157°/748 mm.; $d_4^{25°}$ 1·1196; $\eta_{25°}$ 2·488 centipoise (Found: SH, 39·6. Calc. for C_2H_6OS: SH, 39·8%).

Thiodiglycol from 2-Hydroxyethanethiol.—Ethylene chlorohydrin (20 g., 0·25 mol.) and 2-hydroxyethanethiol (19·5 g., 0·25 mol.) were heated over the steam-bath for 5 hours with sodium carbonate

(26 g.). After filtration, the reaction product was distilled, and after removal of some of the unreacted starting material, 2 : 2′-dihydroxydiethyl sulphide was obtained, b. p. 146°/7 mm., in 50% yield.

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H.M. Research Establishment, Sutton Oak. [*Received, October 8th,* 1947.]

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380. *Some Reactions of Ethylene Sulphide, and a New Method of Preparation of Vicinal Dithiols.*

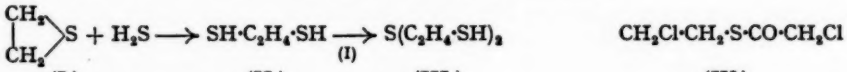
By E. M. Meade and F. N. Woodward.

Ethylene sulphide (I) has been shown to resemble ethylene oxide in many of its reactions. The ring is easily opened by the action of hydrogen chloride, chloroacetyl chloride and bromide, methane- and *n*-pentane-thiol, and hydrogen sulphide to give 2-chloroethanethiol, 2-chloro- and 2-bromo-ethylthiolochloroacetate, 2-methyl- and 2-*n*-amyl-thioethanethiols, and a mixture of ethylene dithiol (II) and 2 : 2′-dimercaptodiethyl sulphide (III), respectively. The last reaction can be modified for the continuous production of (II).

Ethylene sulphide, prepared by the interaction of chloroethyl thiocyanate and aqueous sodium sulphide (Delépine, *Compt. rend.*, 1920, **171**, 36), of 2-chloroethanethiol and aqueous sodium hydrogen carbonate (U.S.P. 2,183,860), or of thiourea or a water-soluble thiocyanate and ethylene oxide in the presence of an alkali chloride or carbonate (U.S.P. 2,094,837; Canad. P. 392,681; B.P. 465,662), has been but little investigated.

Delépine and Eschenbrenner (*Bull. Soc. chim.*, 1923, **33**, 703) found that (I) resembles ethylene oxide in many of its reactions. Nitric acid oxidised it to the acids $SO_3H{\cdot}CH_2{\cdot}CO_2H$ and $SO_3H{\cdot}[CH_2]_2{\cdot}S{\cdot}CH_2{\cdot}CO_2H$, and excess of hydrochloric acid yields a mixture of 2-chloroethanethiol, 2-chloroethylthioethanethiol, and dithian. Similarly, hydrobromic acid affords 2-bromoethanethiol.

In view of the known ease of opening of the ethylene oxide (preceding paper) and the ethyleneimine ring (*Ber.*, 1897, **30**, 2497) by the action of hydrogen sulphide, it was considered probable that (I) would behave similarly to afford (II) and (III) :



(I.) (II.) (III.) (IV.)

This was found to be the case, the reaction going smoothly in methanol solution at 60°. The yields obtained in a single experiment were 49% of (II), 16% of (III), and 4% of residue [calculated as $(\cdot CH_2{\cdot}S{\cdot}C_2H_4{\cdot}SH)_2$]. The reaction was also carried out satisfactorily with stirring in the continuous convertor described in the preceding paper, affording a 50% yield of (II) when thiodiglycol was used as solvent. The physical characteristics of (I), (II), and (III) have been determined, as have those of 2-chloroethanethiol, which is more readily obtained by the interaction of (I) with hydrogen chloride than by means of hydrochloric acid as advocated by Bennett (*J.*, 1922, **121**, 2139); it was found to be much more stable than previously recorded by Bennett and by Delépine and Eschenbrenner. (I) reacts with sodium *n*-amyl sulphide to give a mixture of 2-n-*amylthioethanethiol* (75%) and what is presumably 2-n-*amylthioethylthioethanethiol*, $C_5H_{11}{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}SH$ (25%). With sodium methyl sulphide, 2-methylthioethanethiol is formed, whilst with chloroacetyl chloride or bromide, 2-*chloroethyl thiolo-chloroacetate* (IV) and -bromoacetate are produced.

Experimental.

Ethylene Sulphide (I).—Prepared essentially as described in B.P. 465,662, from ethylene oxide (60 g). and potassium thiocyanate (90 g.) in water (90 g.) at −5° to −10°, (I) was obtained in 27% yield, b. p. 54—55·5°, and had the following characteristics : $d_4^{20°}$ 1·0113, $n_D^{20°}$ 1·4946, $[R_L]_D$ 17·32 (Calc. : 17·21) (Found : S, 52·7. Calc. for C_2H_4S : S, 53·2%).

2-Chloroethanethiol.—Pure distilled (I) (12 c.c.) in dry ether (200 c.c.) was saturated with dry hydrogen chloride during 20 mins. at −10°. After removal of the solvent, the residue distilled at about 80°/290 m m. On redistillation, 8 g. of the chlorothiol were obtained, b. p. 113—113·5°/760 mm. having the following physical characteristics : $d_4^{20°}$ 1·1826, $n_D^{20°}$ 1·4929, $[R_L]_D$ 23·86 (Calc. : 23·99) (Bennett, *loc. cit.*, gives b. p. 125—126°, $d_4^{20°}$ 1·203, $n_D^{20°}$ 1·5289, $[R_L]_D$ 24·74) (Found : SH, 34·0; Cl, 36·8. Calc. for C_2H_5ClS : SH, 34·2; Cl, 36·8%).

2-Chloroethyl Thiolochloroacetate.—To distilled (I) (6 c.c.) in ether (25 c.c.) was added chloroacetyl chloride (8·4 c.c.) and the mixture refluxed for 2½ hrs. After removal of solvent, the product was distilled, and the middle fraction (8·1 g.), b. p. 85—90°/3 mm., was redistilled to give the pure *ester*, b. p.

83°/3 mm. It had the following characteristics: $d_4^{20°}$ 1·3917, $n_D^{20°}$ 1·5295, $[R_L]_D$ 38·74 (Calc.: 38·39) (Found: Cl, 40·7, 40·9. $C_4H_8OCl_2S$ requires Cl, 41·0%).

2-*Bromoethyl Thiolochloroacetate*.—This ester, b. p. 107—110°/7 mm., prepared similarly from chloroacetyl bromide, had $d_4^{20°}$ 1·6965, $n_D^{20°}$ 1·5603, $[R_L]_D$ 41·46 (Calc.: 41·43).

2-n-*Amylthioethanethiol*.—Distilled (I) (1·1 g.), sealed in a glass ampoule, was broken under a solution of *n*-pentanethiol (3 g.) in alcoholic sodium ethoxide (Na, 0·6 g; EtOH, 25 c.c.). The reaction was exothermic, and after 0·5 hr., glacial acetic acid (4 c.c.) was added together with water (75 c.c.). The aqueous solution was extracted with chloroform, and the chloroform layer was dried and distilled, giving 1·02 g. of impure *thiol*, b. p. 105°/5 mm. (Found: SH, 38·3. $C_7H_{16}S_2$ requires SH, 40·2%), and 0·33 g. of a liquid, b. p. 150°/4 mm.

2-*Methylthioethanethiol*.—A mixture of (I) in twice its volume of alcohol and a 150% excess of sodium methyl sulphide in alcohol was refluxed for 0·25 hr., and the solvent removed by distillation. The residue after cooling and acidification (dilute acetic acid) was extracted with chloroform. After removal of the solvent from the extract, distillation gave the *thiol*, b. p. 82°/40 mm., in 40% yield (Found: SH, 30·5. $C_3H_8S_2$ required SH, 30·5%).

Ethylenedithiol (II) *and* 2 : 2′-*Dimercaptodiethyl Sulphide* (III).—Methanol (750 c.c.) was saturated (3·5N) with hydrogen sulphide at room temperature, the solution made up to 1 l. (1·32 g.-mol. of H_2S), and (I) (48 g.; 0·8 g.-mol.) added. The mixture was heated at 60° for two days (time required for complete reaction as indicated by pressure change) in a stoppered bottle fitted with a sealed manometer. After removal of the alcohol, distillation gave (*a*) 36·9 g., b. p. 60°/43 mm. to 80°/10 mm.; (*b*) 9·5 g., b. p. 80°/10 mm. to 140°/12 mm.; (*c*) an undistillable residue (2·2 g.). Fraction (*a*) on redistillation gave (II), b. p. 65°/44 mm., 73°/61 mm., $d_4^{24°}$ 1·1200, $n_D^{20°}$ 1·5497, $[R_L]_D$ 26·70 (Calc.: 26·82) (Fasbender, *Ber.*, 1887, **20**, 461, gives b. p. 148°, $d_4^{24°}$ 1·123), in 49% yield (Found: SH, 67·8. Calc. for $C_2H_6S_2$: SH, 68·9%); and fraction (*b*) gave (III), b. p. 102—107°/3 mm., $d_4^{20°}$ 1·1662, $n_D^{20°}$ 1·5807, $[R_L]_D$ 44·08 (Calc.: 44·02) (Meadow and Reid, *J. Amer. Chem. Soc.*, 1934, **56**, 2177, give b. p. 135—136°/10 mm., m. p. −12·5°), in 15% yield (Found: S, 63·0. Calc. for $C_4H_{10}S_3$: S, 63·4%).

When (I), dissolved in thiodiglycol (200 c.c.), was subjected to a stream of hydrogen sulphide (10 l./hr.) at 45° and stirred in the reaction vessel described in the preceding paper, (II) was obtained continuously (50% yield); b. p. 85°/120 mm., 145°/760 mm.

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H.M. Research Establishment, Sutton Oak. [*Received, October 8th*, 1947.]

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381. *Cyanine Dyes from 2 : 3-Dihydro-β-quinindene.*

By A. B. Lal and V. Petrow.

Symmetrical *carbocyanines* (IV*a*; IV*b*) have been prepared from 2 : 3-dihydro-β-quinindene alkiodides. Unsymmetrical *carbocyanines* (V—X*b*) have also been obtained where the second nucleus is derived from trimethylindolenine, quinaldine, 6-methylquinaldine, lepidine, 2-methylbenzoxazole, and 2-methylbenzthiazole.

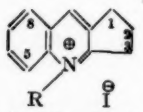
Incidental observations recorded include the conversion of dihydro-β-quinindene methiodide into a *dimethylamino-anil* (II) and a *ψ-cyanine* (III), and the preparation of the p-*dimethylamino-benzylidene* derivative (XII) from 2 : 4-diphenyldihydropyrindene methiodide.

The preparation of cyanine dyes from bases with reactive homocyclic methylene groups, or from their quaternary salts, does not appear to have received much attention hitherto. The possibility of obtaining such compounds was nevertheless foreshadowed in an earlier publication (Petrow, *J.*, 1945, 18), and has now been realised by their synthesis from 2 : 3-dihydro-β-quinindene.

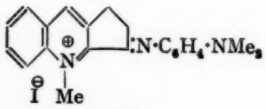
Earlier attempts to condense dihydro-β-quinindene methiodide (I) with *p*-nitrosodimethylaniline in the presence of piperidine were not successful, only black amorphous precipitates being obtained (Petrow, *loc. cit.*). We now find the reaction follows the expected pattern when carried out under carefully controlled conditions giving the 3-p-*dimethylamino-anil* (II) of dihydro-β-quinindene methiodide in excellent yield. This compound is not very stable, however, being decomposed by acids and alkalis, and even on heating in alcoholic solution. Similar instability was encountered in the preparation of a *ψ*-cyanine from dihydro-β-quinindene. Although condensation of (I) with 2-iodoquinoline methiodide and alkali in alcoholic solution (see Hamer, *J.*, 1928, 206) gave [2-(1-*methylquinoline*)][3-(4-*methyldihydro-β-quinindene*)]*cyanine iodide* (III) in moderate yield, yet its purification was handicapped by its partial decomposition on crystallisation, and satisfactory analytical figures for it could not be obtained.

Carbocyanines of the dihydro-β-quinindene series, in contrast, were both stable and well-defined compounds. *Bis*-[4-*methyl*-3-(*dihydro-β-quinindene*)]*methincyanine iodide* (IV*a*), contaminated with a persistent impurity probably of the neocyanine type, was obtained when (I) was heated with ethyl orthoformate in pyridine–acetic anhydride, but was obtained analytically pure from a reaction mixture containing sodium formate and ethyl orthoformate in boiling acetic

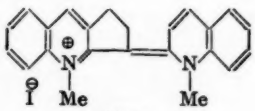
anhydride–pyridine. Essentially the same conditions were employed for converting *dihydro*-β-*quinindene ethiodide* (I*a*) into the *carbocyanine* (IV*b*) except that the addition of the sodium formate proved unnecessary.



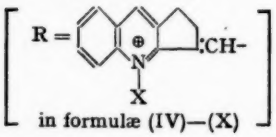
(I; R = Me.)
(I*a*; R = Et.)



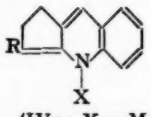
(II.)



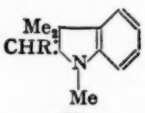
(III.)



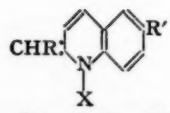
in formulæ (IV)—(X)



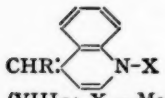
(IV*a*; X = Me.)
(IV*b*; X = Et.)



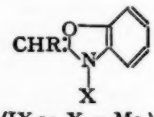
(V.)



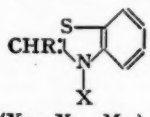
(VI*a*; R′ = H, X = Me.)
(VI*b*; R′ = H X = Et.)
(VII; R′ = X = Me.)



(VIII*a*; X = Me.)
(VIII*b*; X = Et.)

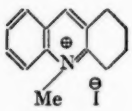


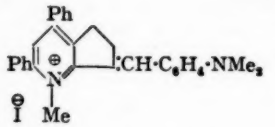
(IX*a*; X = Me.)
(IX*b*; X = Et.)



(X*a*; X = Me.)
(X*b*; X = Et.)

(XI.)





(XII.)

Condensation of (I) with diphenylformamidine by the method of Piggott and Rodd (B.P. 344,409) gave 3-*anilinomethylenedihydro*-β-*quinindene methiodide*, but this intermediate proved unsuitable for the preparation of unsymmetrical carbocyanines. These were ultimately prepared by the reverse procedure, *i.e.*, the condensation of the quinindene alkiodide with the quaternary salt of the appropriate anilinovinyl compound in boiling acetic anhydride–pyridine. The *carbocyanines* (V—X*b*) were obtained in this way from (I; I*a*) and the anilinovinyl salts prepared from trimethylindolenine, quinaldine, 6-methylquinaldine, lepidine, 2-methylbenzoxazole, and 2-methylbenzthiazole. (I) failed to react with 3-*methyl*-2-β-*anilinovinylbenziminazole methiodide*.

Attempts to repeat some of the above preparations using tetrahydroacridine methiodide (XI) in place of (I) were not successful; (XI) failed to react with ethyl orthoformate under a variety of experimental conditions. Although it gave a deep green coloration when heated with chloroform and alkali in alcoholic solution, yet attempts to isolate a crystalline dye from the product were not successful. The methiodide (XI) also failed to react with diphenylformamidine on prolonged heating at 125°, and with 2-*acetanilidovinylbenzoxazole methiodide* in pyridine–acetic anhydride. Vigorous reaction occurred when (XI) was treated with *p*-nitrosodimethylaniline and piperidine in alcoholic solution, but only black amorphous solids were isolated from the intensely purple products. This result would appear to indicate that steric considerations and not a low reactivity of the 1-methylene grouping are responsible for the failure to convert tetrahydroacridine methiodide (XI) into compounds of the cyanine type.

Preliminary experiments on the preparation of cyanine dyes from 2 : 4-diphenyldihydropyrindene methiodide gave discouraging results, only the corresponding 7-p-*dimethylaminobenzylidene* derivative (XII) being obtained. These failures are doubtless due to the lowered reactivity of the 7-methylenic grouping owing to the effect of the 2- and 4-phenyl residues on the ring nitrogen. As attempts to prepare the ethiodide of the parent base were likewise unsuccessful, further experiments in this direction were abandoned.

The photographic properties of the above dyes, kindly determined by Messrs. Kodak Ltd. through the courtesy of Dr. F. M. Hamer, M.A., D.Sc., F.R.I.C., will be reported elsewhere.

Experimental.

(M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.)

2 : 3-*Dihydro*-β-*quinindene ethiodide* (I*a*), light yellow plates from ethyl alcohol, m. p. 206—207° (Found : N, 4·1; I, 39·0. $C_{14}H_{16}NI$ requires N, 4·3; I, 39·1%), was prepared by heating the components for 4 hours on the water-bath.

2-β-Anilinovinylquinoline ethiodide formed yellowish-brown platelets from spirit, m. p. 277—278° (Found : N, 7·0; I, 31·8. Calc. for $C_{19}H_{19}N_2I$: N, 7·0; I, 31·6%) (cf. Piggott and Rodd, *loc. cit.*).

4-β-Anilinovinylquinoline methiodide, red silky needles from spirit, m. p. 259—260° (Found : N, 7·4; I, 32·3. Calc. for $C_{18}H_{17}N_2I$: N, 7·4; I, 32·8%), was obtained (62%) by fusing lepidine methiodide (3 g.) with diphenylformamidine (2 g.) at 160—165° for one hour, followed by trituration of the melt with dilute hydrochloric acid (cf. Piggott and Rodd, *loc. cit.*).

6-*Methyl*-2-β-*anilinovinylquinoline methiodide*, yellowish needles from spirit, m. p. 270° (decomp.) (Found : N, 6·2; I, 32·1. $C_{19}H_{19}N_2I$ requires N, 6·9; I, 31·6%), was obtained (60%) by heating an intimate mixture of *p*-toluquinaldine methiodide (6 g.) and diphenylformamidine (4 g.) at 160° for 15 minutes.

3-*Methyl*-2-β-*anilinovinylbenziminazole methiodide*, light yellow needles from absolute alcohol, m. p. 273° (Found : N, 10·8. I, 32·4. $C_{17}H_{18}N_3I$ requires N, 10·8; I, 32·5%), was obtained (27%) by heating 2 : 3-dimethylbenziminazole (2·7 g.) and diphenylformamidine (2 g.) at 130—135° for 3 hours.

3-β-*Anilinomethylenedihydro*-β-*quinindene methiodide*, dark red prisms from absolute alcohol, m. p. 252° (decomp.) (Found : N, 6·3; I, 30·5. $C_{20}H_{19}N_2I$ requires N, 6·8; I, 30·7%), was obtained (33%) by heating dihydro-β-quinindene methiodide with diphenylformamidine at 111—115° for 2 hours.

2-β-*Acetanilidovinylbenzoxazole methiodide*, bright yellow needles from ethyl acetate–alcohol, m. p. 238—239° (Found : C, 51·2; H, 4·0; N, 6·9; I, 29·2. $C_{18}H_{17}O_2N_2I$ requires C, 51·4; H, 4·0; N, 6·7; I, 30·2%), was obtained (60%) by heating 2-methylbenzoxazole methiodide (11 g.), diphenylformamidine (8 g.), and acetic anhydride (50 ml.) under reflux for 30 minutes, and setting the product aside overnight.

2-β-*Acetanilidovinylbenzthiazole methiodide*, brownish-black prisms from absolute alcohol, m. p. 226° (Found : S, 7·9. $C_{18}H_{17}ON_2IS$ requires S, 7·4%), was prepared as for the oxygen analogue above.

3-p-*Dimethylaminoanil of Dihydro*-β-*quinindene Methiodide* (II).—Dihydro-β-quinindene methiodide (I) (1·6 g.) in hot absolute alcohol (50 ml.) was treated with *p*-nitrosodimethylaniline (900 mg.) in hot absolute alcohol (25 ml.), followed by immediate addition of piperidine (0·5 ml.). After 10 minutes' heating the *dye* was collected and crystallised from methyl alcohol, from which it separated (48%) in dark green needles, m. p. 212° (Found : N, 9·3; I, 28·4. $C_{21}H_{22}N_3I$ requires N, 9·5; I, 28·7%).

[2-(1 : 3 : 3-*Trimethylindolenine*)][3-(4-*methyldihydro*-β-*quinindene*)]*dimethincyanine* (V), brown microcrystals (90%) from spirit, m. p. 264—265° (Found : N, 5·8; I, 25·8. $C_{25}H_{27}N_2I$ requires N, 5·6; I, 25·7%), was obtained when an intimate mixture of (I) (2·1 g.), 3 : 3-dimethyl-2-β-acetanilidovinylindolenine methiodide (2·1 g.), and potassium acetate (2 g.) was added to acetic anhydride (50 ml.) and pyridine (5 ml.), the mixture heated under reflux for 1 hour, and the dye precipitated with water (400 ml.).

[2-(1-*Methylquinoline*)][3-(4-*methyldihydro*-β-*quinindene*)]*cyanine Iodide* (III).—Dihydro-β-quinindene methiodide (1·5 g.) and 2-iodoquinoline methiodide (2 g.) in absolute alcohol (100 ml.) were treated with potassium hydroxide (700 mg.) under reflux. After 30 minutes the product was poured into water (400 ml.). After standing overnight the *dye* was collected and purified from aqueous alcohol, giving dark violet prisms (45%), m. p. 242—243° (decomp.) (Found : I, 25·2. $C_{23}H_{21}N_2I,C_2H_5{\cdot}OH$ requires I, 25·5%).

Bis-[4-*methyl*-3-(*dihydro*-β-*quinindene*)]*methincyanine Iodide* (IV*a*).—Dihydro-β-quinindene methiodide (2 g.), sodium formate (1 g.), ethyl orthoformate (2 g.), acetic anhydride (20 ml.), and pyridine (5 ml.) were heated under reflux for 15 minutes. After standing overnight at room temperature, the *dye* was collected and crystallised from pyridine, giving bronze platelets (20%), m. p. 268° (decomp.) (Found : N, 5·3; I, 25·2. $C_{27}H_{25}N_2I$ requires N, 5·6; I, 25·2%).

Bis-[4-*ethyl*-3-(*dihydro*-β-*quinindene*)]*methincyanine iodide* (IV*b*), copper plates from pyridine, m. p. 270° (decomp.) (Found : N, 5·4; I, 23·8. $C_{29}H_{29}N_2I$ requires N, 5·3; I, 23·9%), was obtained (30%) by heating dihydro-β-quinindene ethiodide (2·2 g.) and ethyl orthoformate (2·3 g.) in pyridine (20 ml.) and acetic anhydride (5 ml.) for 1 hour.

[2-(1-*Methylquinoline*)][3-(4-*methyldihydro*-β-*quinindene*)]*dimethincyanine iodide* (VI*a*), lustrous violet plates (30%) from pyridine, m. p. 272—273° (Found : C, 62·4; H, 4·9; N, 5·8. $C_{25}H_{23}N_2I$ requires C, 62·7; H, 4·9; N, 5·9%), was prepared by heating dihydro-β-quinindene methiodide (1·4 g.), 2-β-anilinovinylquinoline methiodide (1·4 g.), sodium acetate (2 g.), acetic anhydride (50 ml.), and pyridine (5 ml.) under reflux for 1 hour, followed by precipitation with water (500 ml.).

[2-(1-*Ethylquinoline*)][3-(4-*ethyldihydro*-β-*quinindene*)]*dimethincyanine iodide* (VI*b*), dark green, lustrous plates (52%) from pyridine, m. p. 284—285° (decomp.) (Found : N, 5·6; I, 25·3. $C_{27}H_{27}N_2I$ requires N, 5·5; I, 25·1%), was prepared by heating (I*a*) (1·3 g.), 2-β-anilinovinylquinoline ethiodide (1·6 g.), sodium acetate (2 g.), and acetic anhydride (30 ml.) under reflux for 1 hour, followed by precipitation of the dye with water (400 ml.).

[2-(1 : 6-*Dimethylquinoline*)][3-(4-*methyldihydro*-β-*quinindene*)]*dimethincyanine iodide* (VII), prepared as for (VI*a*) but using 2-β-anilinovinyl-6-methylquinoline methiodide, formed violet plates (25%) from pyridine, m. p. 269—270° (decomp.) (Found : N, 6·0; I, 25·5. $C_{26}H_{25}N_2I$ requires N, 5·7; I, 25·8%).

[4-(1-*Methylquinoline*)][3-(4-*methyldihydro*-β-*quinindene*)]*dimethincyanine iodide* (VIII*a*), lustrous green platelets from pyridine, m. p. 264—265° (Found : N, 6·1; I, 26·1. $C_{25}H_{23}N_2I$ requires N, 5·9; I, 26·5%), was obtained (60%) by adding an intimate mixture of (I) (1·5 g.), 4-β-anilinovinylquinoline methiodide (2 g.), and potassium acetate (1·5 g.) to acetic anhydride (50 ml.) and pyridine (5 ml.), and after heating for 1 hour, precipitating the dye with water (500 ml.).

[4-(1-*Ethylquinoline*)][3-(4-*ethyldihydro*-β-*quinindene*)]*dimethincyanine iodide* (VIII*b*), obtained (80%) as for (VIII*a*), formed green, silky needles from spirit, m. p. 277—278° (decomp.) (Found : N, 5·4; I, 25·2. $C_{27}H_{27}N_2I$ requires N, 5·5; I, 25·1%).

[2-(3-*Methylbenzoxazole*)][3-(4-*methyldihydro*-β-*quinindene*)]*dimethincyanine iodide* (IX*a*), dark violet

prisms from pyridine, m. p. 267—268° (Found: N, 5·9; I, 27·0. $C_{23}H_{21}ON_2I$ requires N, 6·0; I, 27·1%), was obtained (60%) by heating (I) (1·6 g.), 2-β-acetanilidovinylbenzoxazole methiodide (2·1 g.), sodium acetate (2·5 g.), and acetic anhydride (40 ml.) for 1 hour, followed by precipitation of the dye with water (500 ml.).

[2-(3-*Ethylbenzoxazole*)][3-(4-*ethyldihydro-β-quinindene*)]*dimethincyanine iodide* (IX*b*) formed dark violet prisms (63%) from pyridine, m. p. 274—275° (decomp.) (Found: N, 5·8; I, 25·2. $C_{25}H_{25}ON_2I$ requires N, 5·7; I, 25·6%).

[2-(3-*Methylbenzthiazole*)][3-(4-*methyldihydro-β-quinindene*)]*dimethincyanine iodide* (X*a*) formed dark green plates (60%) from pyridine, m. p. 271° (Found: N, 5·7; I, 25·6. $C_{23}H_{21}N_2IS$ requires N, 5·8; I, 26·2%).

[2-(3-*Ethylbenzthiazole*)][3-(4-*ethyldihydro-β-quinindene*)]*dimethincyanine iodide* (X*b*) formed lustrous green prisms (60%) from pyridine, m. p. 279° (Found: N, 5·2; I, 24·5. $C_{25}H_{25}N_2IS$ requires N, 5·5; I, 24·8%).

3-p-*Dimethylaminobenzylidene*-2 : 3-*dihydro-β-quinindene ethiodide*, blue needles from absolute alcohol, m. p. 221—222° (decomp.) (Found: N, 6·3; I, 27·8. $C_{33}H_{35}N_2I$ requires N, 6·1; I, 27·9%), was obtained (85%) by adding an intimate mixture of (I*a*) (1 g.) and *p*-dimethylaminobenzaldehyde (500 mg.) to boiling acetic anhydride (15 ml.) and, after a further 4 minutes' heating, allowing the solution to cool and collecting the dye.

The 7-p-*dimethylaminobenzylidene* derivative of 2 : 4-diphenyldihydropyrindene methiodide (XII), red silky needles from absolute alcohol, m. p. 184—185° (decomp.) (Found: N, 4·8; I, 22·9. $C_{30}H_{29}N_2I$ requires N, 5·2; I, 23·3%), was obtained (30%) when 4 : 6-diphenyl-2 : 3-trimethylenepyridine methiodide (1·0 g.), *p*-dimethylaminobenzaldehyde (400 mg.), piperidine (0·5 ml.), and absolute alcohol (25 ml.) were heated under reflux for 15 hours, alcohol (15 ml.) removed by distillation, and the residue allowed to crystallise.

One of us (A. B. L.) thanks the Government of Bihar, India, for a State Scholarship.

QUEEN MARY COLLEGE (UNIVERSITY OF LONDON), E.1. [*Received, December 29th* 1947.]

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382. *The Thermal Decomposition of Lead Oxalate.*

By L. L. BIRCUMSHAW and IVAN HARRIS.

The kinetics of the decomposition of lead oxalate has been investigated at 309°, 325°, 335°, and 350°. The whole range of the decomposition is most adequately expressed by the equation $\log_e x/(1-x) = kt + C$, where x is the fraction decomposed at the time t. The effect of fine grinding on the material is to remove any induction period and reduce slightly the acceleration period, as interference between chains commences sooner. Evidence is brought forward to show that the decomposition is probably catalysed by the solid products of the reaction. The energy of activation for both the accelerating and the decay period is 36 k.-cals.

A CONSIDERABLE amount of experimental work on the kinetics of the thermal decomposition of crystalline solids has been carried out and the general characteristics of the type of reaction Solid ⟶ Solid + Gas are now moderately well known. Bright and Garner (*J.*, 1934, 1872), Garner and Southon (*J.*, 1935, 1705), and Cooper and Garner (*Trans. Faraday Soc.*, 1936, **32**, 735) have demonstrated the formation of nuclei in the dehydration of salt hydrates and have studied their rates of growth. The decomposition of explosive solids such as lead azide (Garner and Gomm, *J.*, 1931, 2123) and mercury fulminate (Garner and Hailes, *Proc. Roy. Soc.*, 1933, *A*, **139**, 576) has also been investigated, and in order to explain some of the results Garner has put forward his " branching-chain theory " of solid decomposition. This theory has been criticised by MacDonald (*J.*, 1936, 832, 839) as the result of some work on the thermal decomposition of silver oxalate, mainly on the ground that decomposition along a network of lines of weakness in the crystal, *e.g.*, Smekal cracks, could only account for the decomposition of a small fraction of the whole solid. MacDonald put forward an alternative theory of planar nuclei to account for his results. Quite recently the branching theory has been extended by Prout and Tompkins (*Trans. Faraday Soc.*, 1944, **40**, 488) in a reinvestigation of the velocity of thermal decomposition of potassium permanganate and of silver permanganate (*ibid.*, 1946, **42**, 468). This theory probably provides a better physical basis for the branching theory and also takes into account the interference of the chains. The results embodied in the present communication are shown to be in general agreement with this theory. It has been shown (Bircumshaw and Harris, *J.*, 1939, 1637) that lead oxalate decomposes according to the equation $3Pb(OOC)_2 \longrightarrow 2PbO + Pb + 4CO_2 + 2CO$. The change is endothermic.

EXPERIMENTAL.

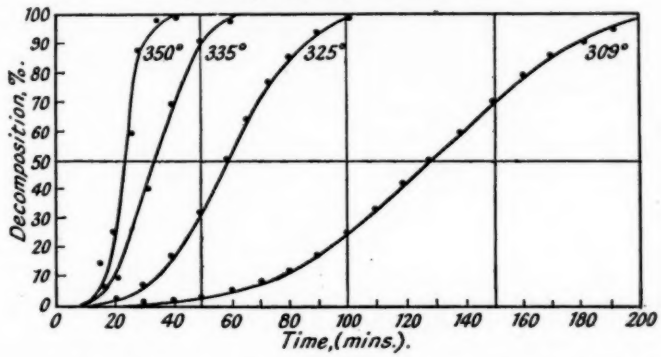
The lead oxalate used was prepared from " A.R. " reagents by precipitation from N/5-sodium oxalate solution with N/5-lead nitrate solution. Precipitation was carried out with boiling solutions and after filtration the precipitate was washed, dried at 100°, and stored in a vacuum desiccator.

The apparatus used for determining the rates consisted of a Pyrex-glass reaction tube connected to the usual pumping system consisting of a mercury diffusion pump backed by a Cenco pump. Pressure changes were measured with a McLeod gauge. Samples of the lead oxalate were placed in a small porcelain boat inside the reaction tube. The latter could be rapidly enclosed by a small electric tube furnace which was mounted on a " railway." The temperature was measured with a calibrated thermocouple placed inside the reaction tube. At suitable times the pumps were cut off, and the pressure allowed to rise for a given time (30 secs.). This rise gave the rate in arbitrary units which could be converted into suitable units (% decomp./min.) by graphical integration.

Results.—The plots of the fraction of lead oxalate decomposed against time (mins.) are shown in Fig. 1 and are of the usual sigmoid type. Four separate curves are given at temperatures 309°, 325°, 335°, and 350° respectively. The values of x, the fraction decomposed, were obtained by plotting the rate of decomposition measured in arbitrary pressure units against the time in minutes and integrating by square counting. The total area corresponds, of course, to 100% decomposition, and by dividing the area at any given time by the total area the fraction decomposed at this time was obtained. From these values the rates of decomposition can be expressed in percentage decomposed/min.

FIG. 1.

Decomposition of lead oxalate.



From these results the general validity of the well-known equations derived from the branching theory was examined :

$$\log_e x = kt + C \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

$$\log_e (dx/dt) = kt + C \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

In both cases a plot of log x or log dx/dt against time would give a straight line. This has been done (on semi-log paper) and it is seen that the equations hold almost up to the time of half decomposition (Figs. 2 and 3). The validity of the following equations has also been tested :

$$dx/dt = kt^m \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$dx/dt = kx^{2/3} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

by plotting log dx/dt against log t and against log x. Both equations are deduced on the assumption that the reaction spreads spherically into the body of the solid. Garner has shown that the maximum value of m in equation (3) should be 3·0. In equation (4) the slope should of course be $\frac{2}{3}$. Neither equation holds in this case and it is concluded that the simple interface theory does not apply. Garner has found that the final stages in some solid decompositions (*e.g.*, of mercury fulminate) obey a unimolecular law, and this has been found to be the case over a limited range with lead oxalate.

The values at all four temperatures of the two constants (min.$^{-1}$) are given in Table I.

TABLE I.

Temp.	Unground $Pb(OOC)_2$.	Ground $Pb(OOC)_2$.	Temp.	Unground $Pb(OOC)_2$.	Ground $Pb(OOC)_2$.
	Equation : $\log_e dx/dt = kt + C$.			Equation : $\log_e x = kt + C$.	
309°	$4{\cdot}2 \times 10^{-2}$		309°	$6{\cdot}5 \times 10^{-2}$	
325	$1{\cdot}09 \times 10^{-1}$	$1{\cdot}32 \times 10^{-1}$	325	$9{\cdot}5 \times 10^{-2}$	$3{\cdot}45 \times 10^{-1}$
335	$1{\cdot}92 \times 10^{-1}$		335	$1{\cdot}84 \times 10^{-1}$	
350	$2{\cdot}43 \times 10^{-1}$		350	$2{\cdot}4 \times 10^{-1}$	

In Fig. 6, the rate–time curves at 325° for lead oxalate, ground and unground, are compared. It will be seen that grinding removes practically the whole of the induction period, in this case 6—7 minutes.

The equations based on the simple branching theory appear to break down just before the maximum rate of decomposition is reached; one possible cause of this may be the interference of the chains, and this effect has been taken into account by Prout and Tompkins in discussing the results of their work on potassium and silver permanganates. They find that potassium permanganate decomposes according to the equation

$$\log_e x/(1 - x) = kt + C \, . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

FIG. 2.

Plots of log x against time.

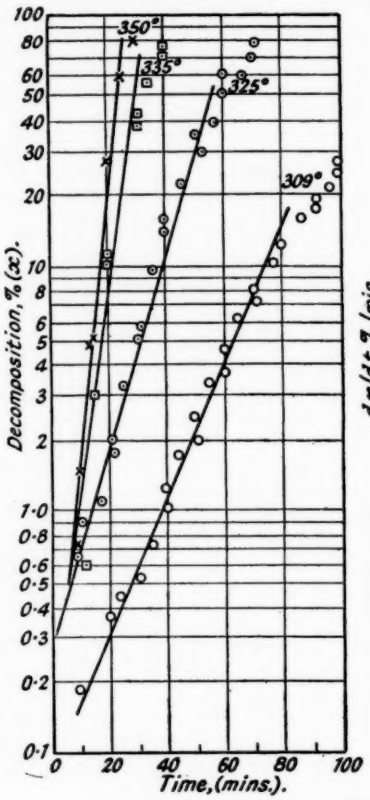


FIG. 3.

Plot of log dx/dt against time.

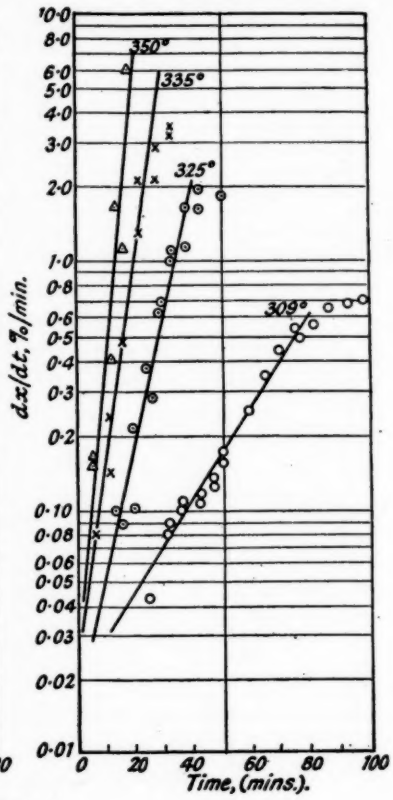
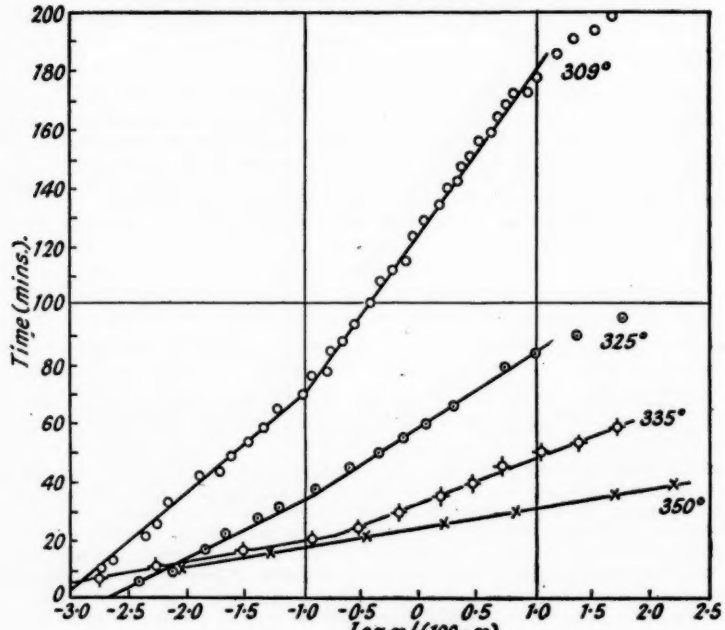


FIG. 4.

Plots of log x/(100 − x) against time.



where x is the fraction decomposed at the time t. To describe the complete course of the decomposition it is necessary to use two constants in the above equation owing to the fact that the sigmoid x–t curves are not symmetrical about the time for maximum rate of decomposition. In Fig. 4 are shown plots of $\log x/(1-x)$ against t from which values of k for both the period of acceleration and the period of decay are obtained. The values are given in Table II.

TABLE II.

	Unground lead oxalate.		Ground lead oxalate.	
Temp.	k (accel.).	k (decay).	k (accel.).	k (decay).
309°	$6{\cdot}45 \times 10^{-3}$	$4{\cdot}15 \times 10^{-2}$		
325	$1{\cdot}73 \times 10^{-1}$	$9{\cdot}0 \times 10^{-2}$	$2{\cdot}09 \times 10^{-1}$	$7{\cdot}81 \times 10^{-2}$
335	$2{\cdot}83 \times 10^{-1}$	$1{\cdot}45 \times 10^{-1}$		
350	$4{\cdot}02 \times 10^{-1}$	$3{\cdot}15 \times 10^{-1}$		

Energy of activation. In Fig. 5 values of $\log k$ taken from Table II are plotted against $1/T$, where T is the absolute temperature. From the slopes of the graphs E is found to be 36,000 cals. for both the acceleration and the decay periods.

FIG. 5.

Energy of activation.

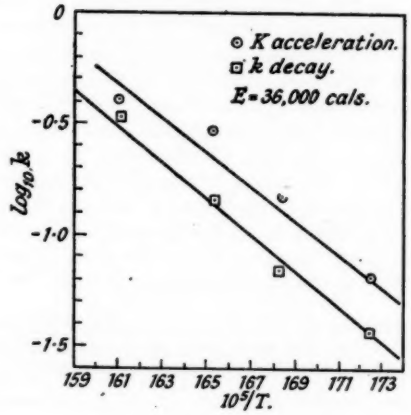
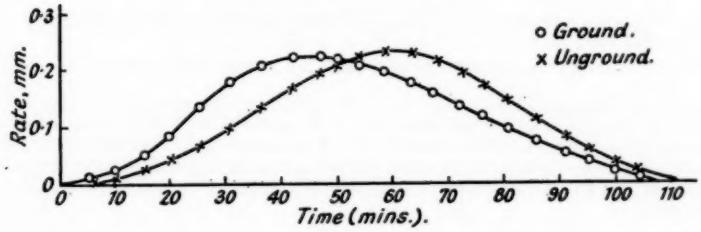


FIG. 6.

Comparison of rate–time curves of ground and unground lead oxalate decomposed at 325°. Excess of nitrate ion.



DISCUSSION.

There is abundant evidence that thermal decomposition in crystalline solids commences from nuclei, the formation and growth of which has in some cases been observed and photographed. The simple equations (3) and (4), which have been deduced on the assumption that the nucleus grows uniformly into the crystal, do not hold in the present case and it is necessary to assume some type of chain mechanism to account for the rapid acceleration of the decomposition in the early stages of the reaction. Garner adopted the idea of a degenerate branching process, but the mathematical treatment given by Semenoff (" Chain Reactions," 1935) makes no distinction between an energy chain and a chain propagated by some intermediate catalyst, *i.e.*, an autocatalytic reaction. The theory put forward by Prout and Tomkins probably represents an advance on the previous chain theory and, moreover, accounts for the whole reaction by assuming that branching occurs as the result of lateral strains set up in the crystal. These

are relieved by the formation of Smekal cracks along which decomposition is favoured and further cracking is produced by more strains caused by the decomposition. The reaction thus spreads deeper into the crystal. Equation (5) represents the course of the whole reaction; but in general two equations each with a different constant (k) will be necessary owing to the asymmetry of the p–t curves. Garner's branching theory might not be expected to hold when individual chains begin to interfere with each other, and this has been found to be the case in the present work. The branching equation begins to fail a little before the time of half decomposition is reached. Similar behaviour was reported by Garner and Hailes in their work on mercury fulminate. They showed also that the second half of the reaction, after the maximum rate had been reached, could be considered as an ordinary unimolecular reaction.

It was not found possible to prepare large crystals of lead oxalate and investigate their decomposition, but a study of the decomposition of the ground salt gives the expected results. The general effect is obviously to increase the initial number of nuclei and thus remove any induction period. The acceleration period is reduced in duration, and interference between the chains commences sooner. Grinding does not, however, produce any great difference in the values of the acceleratory constants.

In the decay period the rate-controlling factor becomes the number of decomposed lead oxalate molecules. The theory put forward by Prout and Tomkins for the decomposition of potassium permanganate indicates that equation (5) will be obeyed in the decay period if it is assumed that decomposition is favoured in those molecules which are adjacent to a molecule of the product. This is the case with lead oxalate; but the same authors have found that with silver permanganate the unimolecular equation $\log_e(P - p) = kt + C$, where P is the final pressure and p the pressure at time t, is more applicable in the decay period. This is in agreement with the experimental observation that the rate of decomposition is not accelerated by the end-products of the reaction; *i.e.*, the silver permanganate molecules decompose without the restriction that they must be adjacent to the product molecules.

In the present work, although there is no direct evidence of the effect of end-products, the good agreement of the results with equation (5) in the decay period would indicate that lead oxalate behaves in a similar way to potassium permanganate.

The authors are greatly indebted to Professor W. E. Garner, F.R.S., for a criticism of the results of this paper. One of them (I. H.) would like to express his grateful thanks to the University College of the South West, Exeter, for the award of a Willey Research Scholarship.

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383. *Derivatives of Trishydroxymethylnitromethane.*

By GODFREY FORT and ANDREW MCLEAN.

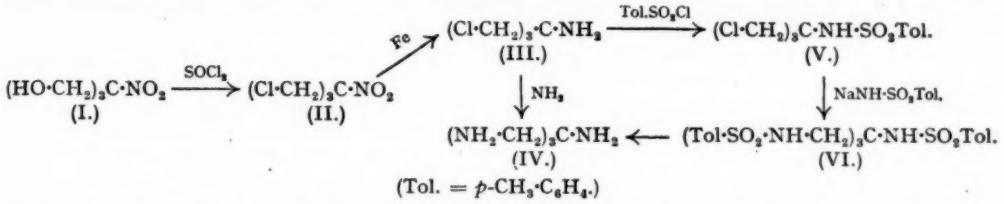
Trischloromethylaminomethane has been obtained in high yield from trishydroxymethylnitromethane and has been converted into the tetramine, $C(CH_2{\cdot}NH_2)_3{\cdot}NH_2$, by two methods. A compound resulting from the self-condensation of trischloromethylaminomethane in presence of alkaline catalysts has been tentatively formulated as 2:2:5:5-tetrakischloromethylpiperazine.

Attempts to prepare the nitroamines $C(CH_2{\cdot}NH{\cdot}NO_2)_3{\cdot}NH{\cdot}NO_2$ and $C(CH_2{\cdot}O{\cdot}NO_2)_3{\cdot}NH{\cdot}NO_2$ were unsuccessful.

THE main part of the present work was the preparation of the tetramine, trisaminomethylaminomethane (IV), for which the starting material was the trichloro-amine (III) previously prepared by Kleinfeller (*Ber.*, 1929, **62**, 1582) from trishydroxymethylnitromethane (I) by successive chlorination with phosphorus pentachloride and reduction with stannous chloride. The following scheme shows two routes employed to prepare the tetramine (IV). Of these, the first was analogous to that employed by Litherland and Mann (*J.*, 1938, 1591) for the preparation of tetrakisaminomethylmethane from tetrakisbromomethylmethane, and the second involved direct ammonolysis in aqueous alcohol. The approximate yield of distilled tetramine by the second method was 50% on trischloromethylaminomethane (28% on trishydroxymethylnitromethane), and by the first about half these values.

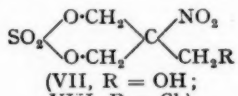
By modifying Kleinfeller's method of preparation, yields of trischloromethylaminomethane as high as 62% on the trishydroxymethylnitromethane were obtained. In the improved method excess of thionyl chloride and pyridine were used for the chlorination, and the

trischloromethylnitromethane (II) was reduced by gradual addition of water to a stirred suspension of iron powder in its benzene solution (Hazlet and Dornfeld, *J. Amer. Chem. Soc.*,

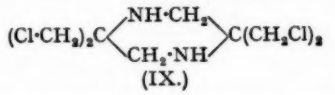


(Tol. = p-$CH_3 \cdot C_6H_4$.)

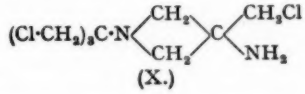
1944, **66**, 1781). With smaller proportions of the chlorinating agents, trishydroxymethylnitromethane yielded, in addition to trischloromethylnitromethane, the cyclic sulphate (VII) previously prepared by Kleinfeller (*loc. cit.*) and also a substance, probably the corresponding *chloride* (VIII), which proved difficult to purify owing to solvation.



(VII, R = OH; VIII, R = Cl.)



(IX.)

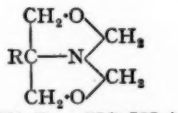


(X.)

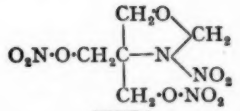
$[(p\text{-}Me\cdot C_6H_4\cdot SO_2\cdot NH)_3C_4H_6]_2NH$
(XI.)

$C(CH_2\cdot NH\cdot NO_2)_3\cdot NH\cdot NO_2$
(XII.)

$[(EtO_2C\cdot NH)_2C_4H_6\cdot NH]_2CO$
(XIII.)



(XIV, R = $HO\cdot CH_2$.)
(XV, = $CH_3\cdot CO_2\cdot CH_2$.)



(XVI.)

Trischloromethylaminomethane was found to be a readily distillable and fairly stable liquid. Kleinfeller does not appear to have distilled it, but recorded that crystals were deposited on standing. This observation was confirmed, and the crystals shown to be trischloromethylaminomethane hydrochloride, indicating a self-condensation. In an isolated case a crystalline *compound* (Y) was deposited under similar conditions. (Y) was also obtained in small yield from the residue from the distillation of trischloromethylaminomethane, and also by prolonged heating of this substance alone or in presence of anhydrous sodium carbonate. (Y) had a composition suggesting that it was formed by intermolecular dehydrochlorination of the trichloro-amine, and it is therefore formulated as (IX). Structure (X) is rejected on account of the less likely four-membered ring. Trischloromethylaminomethane gave Schiff's bases readily with aromatic aldehydes, *e.g.*, *m*-nitro- and *p*-chloro-benzaldehydes.

Initial experiments showed that application of the sodio-toluene-*p*-sulphonamide reaction to trischloromethylnitromethane failed, as had been expected, on account of the lack of reactivity of the chlorine atoms, and that trischloromethylaminomethane reacted violently with decomposition. The *toluene*-p-*sulphonamide* (V), however, reacted smoothly without solvent at 140°, a temperature considerably lower than that required for the highly symmetrical compound $C(CH_2Br)_4$ employed by Litherland and Mann (*loc. cit.*), and gave a 64% yield of the pure *tetratoluene*-p-*sulphonamide* (VI). Hydrolysis with 80% sulphuric acid gave a high yield of the tetramine disulphate from which the free base was liberated. Sodiotoluene-*p*-sulphonmethylamide was also shown to react with the toluene-*p*-sulphonate (V) of trischloromethylaminomethane to give *tris*(*toluene*-p-*sulphonmethylamidomethyl*)*toluene*-p-*sulphonamidomethane*. The tetramine (IV) was more conveniently prepared by heating trischloromethylaminomethane with a large excess of ammonia in aqueous alcohol. It gave a *tetrapicrate* which was difficult to purify and gave rather poor analyses. The residue from the distillation of the crude tetramine gave a crystalline toluene-*p*-sulphonyl compound with the composition of the *hexatoluene*-p-*sulphonyl* derivative (XI) of a secondary amine derived from the tetramine by elimination of ammonia.

The preparation of the tetranitroamine (XII) was attempted by nitration of the *tetraurethane*, a crystalline derivative obtained along with smaller amounts of a higher-melting by-product (probably XIII) by reaction of the tetramine with ethyl chloroformate. The product of nitration under various conditions was a gum which on decarbethoxylation with ammonia gave a hard, colourless glass which could not be purified, and possessed a lower nitrogen value than that for (XII).

A related objective was the preparation of trisnitroxymethylnitroaminomethane. Unpublished work carried out in this laboratory had shown that direct nitration of trishydroxymethylaminomethane did not introduce an *N*-nitro-group but yielded only trisnitroxymethylaminomethane. Activation of the amino-group by carbethoxylation might provide a solution to this problem but was not attempted. Attention was restricted to attempts to nitrate the bicyclic compound (XIV), which by analogy with the production of *cyclo*trimethylenetrinitroamine from hexamine, might have yielded the desired product by fission of both rings and elimination of the methylene groups. Bicyclic compounds of this type have been shown to be formed by a general reaction of 2-nitro-1 : 3-diols with aldehydes (B.P. 564,506; Senkus, *J. Amer. Chem. Soc.*, 1945, **67**, 1515; Hancock *et al.*, *ibid.*, 1944, **66**, 1738, 1747). Nitration of (XIV) failed to yield the required product but gave a small yield of *3-nitro-4 : 4-bisnitroxymethyloxazolidine* (XVI) which resulted from fission of only one ring. Nitration of the bicyclic condensation product (XV) from 1 : 1-bishydroxymethylpropylamine and formaldehyde failed to yield any crystalline product.

Experimental.

Trischloromethylnitromethane (II).—The method of Kleinfeller (*loc. cit.*) gave the compound, m. p. 102—103° (from 70% ethanol), in 26% yield. The following method was more convenient. Thionyl chloride (5% excess) was added during 5—6 hours to a stirred solution of trishydroxymethylnitromethane in pyridine (5% excess) kept at 40—50°. After standing overnight the mixture was heated at 95—100° until sulphur dioxide evolution ceased (½ hour), cooled to *ca.* 35°, and poured into ice–water. The crystalline precipitate was collected and washed with water, and the moist product recrystallised first from ethanol (charcoal), and then from 70% ethanol, yielding the pure compound (needles), m. p. 102—104°; yield 72·5%.

Using crude nitro-alcohol yields were low (40—50%), but were raised to 70% when the chlorinating agents were used in 40% excess.

2-Nitro-2-chloromethyltrimethylene Sulphate (VIII).—Although the above method for the preparation of trischloromethylnitromethane usually gave the results stated when pure trishydroxymethylnitromethane was used, yields were sometimes unaccountably low and, when this occurred, (VIII) could be isolated from the reaction liquors, sometimes as the chief product. Thus in a run carried out as described, recrystallisation of the crude product in turn from ethanol and 70% ethanol gave material of m. p. 50—98°. Three additional recrystallisations from carbon tetrachloride and one from light petroleum gave needles, m. p. 85—88°. Analyses indicated that carbon tetrachloride solvation was very persistent and not readily eliminated by further recrystallisation from non-polar solvents. Sublimation, however, gave the *compound*, m. p. 62°, as a crystalline powder (Found : C, 22·5; H, 2·9; N, 6·0; Cl, 16·8; S, 15·1. $C_4H_6O_5NClS$ requires C, 22·3; H, 2·8; N, 6·5; Cl, 16·5; S, 14·9%). Further recrystallisation from acetone–light petroleum and ethanol (thrice) followed by drying at 60°/6 mm. gave opaque needles, m. p. 86—89° (with softening above 78°) (Found : Cl, 16·4%).

2-Nitro-2-hydroxymethyltrimethylene Sulphate (VII).—This was isolated in an attempted preparation of bischloromethylhydroxymethylnitromethane. Trishydroxymethylnitromethane (0·95 mole), thionyl chloride (2·0 moles), and pyridine (2·1 moles) were brought into reaction under the conditions used for the preparation of trischloromethylnitromethane. Elimination of sulphur dioxide at 95° and pouring into water gave only a small oily precipitate which failed to crystallise and was discarded. The aqueous solution (C) was saturated with sodium sulphate and extracted several times with ether. The ether extracts yielded 36% of the crude sulphate, m. p. 100°, and recrystallisation from benzene, 28%, m. p. 104°. Several recrystallisations from chloroform raised the m. p. to 105—106° (Found: C, 24·4; H, 3·4; N, 6·5; S, 16·7. Calc. for $C_4H_7O_6NS$: C, 24·4; H, 3·6; N, 7·1; S, 16·2%). Further treatment of (C) in a continuous ether extractor gave only a small quantity of unchanged trishydroxymethylnitromethane.

Trischloromethylaminomethane (III).—Iron filings (100 g.; 50 mesh) were stirred with concentrated hydrochloric acid (20 c.c.) while cooled in ice, dried in a vacuum desiccator over calcium chloride, and added rapidly in one portion to a solution of trischloromethylnitromethane (25 g.) in benzene (400 c.c.) in a 3-necked flask fitted with a Hershberg stirrer (*Ind. Eng. Chem. Anal.*, 1936, **8**, 313). Water (40 c.c.) was added in 2 c.c. portions at 15 minute intervals during 4¾ hours, and thereafter refluxing and stirring were continued for 1 hour. The solution was then decanted, the iron sludge washed twice with benzene, and most of the solvent distilled off through an 8 inch packed column. Removal of the remainder of the benzene in a vacuum gave a heavy, pale yellow liquid (19·6 g.; 91·6%) which on distillation gave trischloromethylaminomethane (17·7 g.; 82·5%, b. p. 75—84°/6·5 mm.). The substance deposited crystals on standing (see below).

Other reducing agents gave the following results : (*a*) stannous chloride in ethanol (Kleinfeller, *loc. cit.*) gave a 65% crude yield of amine (isolated by basification and steam-distillation); (*b*) hydrogen and Raney nickel at 3 atmospheres in ethanol gave slow reduction; (*c*) neither the amine nor its hydrochloride was isolated after an attempted reduction with iron and hydrochloric acid in aqueous alcohol.

The hydrochloride separated readily on addition of concentrated hydrochloric acid to the amine, and was purified by recrystallisation from ethanol–acetone. The m. p. 244—246° (decomp.) agrees with that recorded by Kleinfeller (*loc. cit.*). The picrate was prepared by adding light petroleum to an alcoholic solution of equivalent quantities of picric acid and amine in alcohol; m. p. 178° (Kleinfeller, *loc. cit.*, records 180°).

N-m-*Nitrobenzylidene-trischloromethylaminomethane*.—The theoretical quantities of *m*-nitrobenzaldehyde and amine were refluxed in ethanol for 2½ hours. Removal of solvent and recrystallisation from ethanol–light petroleum gave the *Schiff's base* (70·5% yield), m. p. 82—83°; after recrystallised

from the same solvent, m. p. 83—84·5° (Found: C, 42·8; H, 3·8; N, 8·8; Cl, 34·1. $C_{11}H_{11}O_2N_3Cl_3$ requires C, 42·7; H, 3·6; N, 9·0; Cl, 34·4%).

2:2:5:5-*Tetrakischloromethylpiperazine* (IX).—(*a*) Trischloromethylaminomethane (5 g.) was heated at 120° for 7 hours. Filtration and washing with benzene gave trischloromethylaminomethane hydrochloride (1·06 g.), m. p. 260° (decomp.). The washings were evaporated, the residue combined with the filtrate, and the unchanged chloro-amine removed at 100°/44 mm. After being washed with methanol, the crystalline residue (0·24 g.; 12%) melted at 93—100°. For analysis the *piperazine* was recrystallised twice from ethanol–light petroleum and in turn from methanol, benzene, and benzene–light petroleum; m. p. 105—106°, mixed m. p. with trischloromethylnitromethane, 80—94° (Found: C, 34·1; H, 5·0; N, 9·8; Cl, 50·2. $C_8H_{14}N_2Cl_4$ requires C, 34·3; H, 5·0; N, 10·0; Cl, 50·7%).

(*b*) The semi-crystalline residue (5—10 g.) from the distillation of trischloromethylaminomethane (200—300 g.) was purified by recrystallisation from amyl alcohol and extraction with hot carbon tetrachloride. Evaporation of the extract and recrystallisation from 70% ethanol gave crystals melting at 104—106°.

(*c*) Samples of distilled trischloromethylaminomethane deposited crystals of the hydrochloride on standing for several weeks, indicating formation of (IX). In an isolated instance (IX) crystallised in preference to the hydrochloride.

(*d*) Refluxing a 10% solution of the trichloro-amine in toluene for 14 hours in presence of excess of sodium carbonate gave the piperazine derivative in 4·5% yield.

(*e*) Crystals of piperidine hydrochloride were deposited on refluxing a toluene solution of the trichloro-amine and piperidine, but the product was a brittle amber resin from which the piperazine derivative could not be isolated.

Benzoylation.—The substance (IX) (1·26 g.) with benzoyl chloride (1·28 c.c.; 20% excess) and pyridine, gave, on isolation by ether extraction, a crystalline product (0·23 g.) (washed with methanol), m. p. 205—210° (decomp.), and m. p. 210—215° (decomp.) after recrystallisation from glacial acetic acid.

Tosylation.—The substance (IX) (1·146 g.), treated overnight at room temperature with tosyl chloride (1·95 g.; 25% excess) in pyridine, gave a gum which dried to a buff solid (0·944 g.). Crystallisation from aqueous acetic acid gave crystals, m. p. 133—138°, and a mother liquor (D). Three more crystallisations gave the substance as a felted mass of needles of the *monotosyl* derivative, m. p. 138—140° (Found: C, 42·2; H, 4·6; N, 6·5; S, 6·6. $C_{15}H_{20}O_2N_2Cl_4S$ requires C, 41·4; H, 4·6; N, 6·5; S, 7·4%). On standing for several days (D) gave large prisms. Three recrystallisations from glacial acetic acid gave small plates of the *ditosyl* derivative, m. p. 250° (decomp.) (Found: C, 43·2; H, 4·8; N, 4·8; S, 10·7; Cl, 25·1. $C_{22}H_{26}O_4N_2Cl_4S_2$ requires C, 44·9; H, 4·4; N, 4·8; S, 10·9; Cl, 24·2%).

Trischloromethyltoluene-p-*sulphonamidomethane* (V).—Trischloromethylaminomethane (35·05 g.) was dissolved in pyridine (100 c.c.), and tosyl chloride (38·3 g.; slight excess) was added gradually with cooling. After 2 days the mixture was poured into water and the crystalline product collected and washed. The crude product (61·8 g.; 94%), m. p. 121—129°, was purified by one recrystallisation from ethanol and two from carbon tetrachloride, giving pure *compound* (irregular prisms), m. p. 134—135° (Found: C, 40·0; H, 4·3; N, 4·5. $C_{11}H_{14}O_2NCl_3S$ requires C, 40·0; H, 4·3; N, 4·2%).

Tris(*toluene*-p-*sulphonamidomethyl*)*toluene*-p-*sulphonamidomethane* (VI).—Trischloromethyltoluene-*p*-sulphonamidomethane and sodiotoluene-*p*-sulphonamide were brought into reaction under the conditions described by Litherland and Mann (*loc. cit.*) for tetrakisbromomethylmethane but at a lower temperature (140° for 10 hours). The pure *product* (colourless needles; m. p. 197—198°) was obtained by recrystallisation from acetic acid (yield 64%) (Found: C, 52·1; H, 5·1; N, 7·5; S, 17·2. $C_{32}H_{38}O_8N_4S_4$ requires C, 52·3; H, 5·2; N, 7·4; S, 17·4%). Reaction for the same time at 170° and 210° gave yields of 38% and 24% respectively.

Interaction of trischloromethyltoluene-*p*-sulphonamidomethane with toluene-*p*-sulphonamide (3 mols.) in refluxing ethanol for 9 hours in presence of excess of sodium hydroxide (added as 40% solution) gave a 42·4% yield of the tetrakistoluene-*p*-sulphonyl derivative.

Tris(*toluene*-p-*sulphonmethylamidomethyl*)*toluene*-p-*sulphonamidomethane.*—Sodiotoluene-*p*-sulphonmethylamide was prepared by adding toluene-*p*-sulphonmethylamide (25 g.) dissolved in ethanol (75 c.c.) to sodium ethoxide solution (3·7 g. sodium in 88 c.c. ethanol), precipitating by addition of a large volume of ether, and drying in a desiccator.

Equimolar amounts of trischloromethyltoluene-*p*-sulphonamidomethane and sodiotoluene-*p*-sulphonmethylamide were heated at 140° for 10 hours, as for the above preparation of (VI). Recrystallisation from acetic acid (charcoal) gave a product, m. p. 195°, yield 14%. For analysis the *compound* was recrystallised several times from acetic acid (Found: C, 54·5; H, 5·3; N, 7·2; S, 16·4. $C_{35}H_{44}O_8N_4S_4$ requires C, 54·1; H, 5·7; N, 7·2; S, 16·5%).

Trisaminomethylaminomethane Disulphate.—(*a*) Tristoluene-(*p*-sulphonamidomethyl)sulphonamidomethane (8 g.) and 80% sulphuric acid (24 c.c.) were heated for 3 hours at 200° (bath temp.). Pouring into a mixture of water (130 c.c.) and alcohol (65 c.c.) gave the *tetramine disulphate* (2·94 g.; 85·5%), m. p. *ca.* 265° (decomp.). For analysis the substance was purified by several reprecipitations with alcohol from its solution in dilute sulphuric acid and dried at 100°/0·1 mm.; m. p. 280° (decomp.) (Found: C, 15·0; H, 5·5; N, 16·0; S, 21·5. $C_4H_{18}O_8N_4S_2$ requires C, 15·3; H, 5·7; N, 17·8; S, 20·4%).

(*b*) Trischloromethylaminomethane (4 g.) was dissolved in ethanol (23 c.c.), and aqueous ammonia (70 c.c.; *d* 0·88, *i.e.*, 9·3 times theory) added. The solution was heated in an autoclave for 3 hours at 100—110°. Excess of ammonia and part of the solvent were removed under reduced pressure. By addition of sulphuric acid followed by alcohol the tetramine disulphate was precipitated as a liquid which crystallised on standing. (When only 3·3 times the theoretical quantity of ammonia was employed the precipitate did not crystallise even on seeding.) Washed with alcohol, yield 6·45 g. (91%).

Trisaminomethylaminomethane (IV).—(*a*) The tetramine disulphate prepared by ammonolysis of trischloromethylaminomethane was dissolved in hot water and an excess of barium hydroxide solution added. The excess of barium was precipitated by addition of ammonium carbonate. Evaporation of the filtered solution gave the crude tetramine as a viscous, brownish liquid. Yield 95%.

(*b*) A mixture of the crude tetramine disulphate (6·4 g.) and potassium hydroxide (6·4 g.) was extracted

4 times with boiling benzene. Evaporation of the combined extracts gave the crude tetramine. Yield 1·74 g. (73%).

(*c*) The tetramine was most conveniently prepared without previous isolation as the disulphate. A solution containing trischloromethylaminomethane (40 g.), alcohol (300 c.c.), and aqueous ammonia (600 c.c.; *d* 0·88) was heated in an autoclave at 100—110° for 3½ hours and the product evaporated to dryness under reduced pressure. The residue of brown, sticky crystals was mixed with solid sodium hydroxide (54 g.) and repeatedly extracted with boiling toluene. Evaporation of the combined toluene extracts gave the crude tetramine as a brown, viscous liquid (24·0 g., 89·5%). Distillation gave a colourless liquid, b. p. 120°/3—4 mm., containing a small amount of a waxy solid (14·0 g., 52%). A very viscous higher fraction boiled at 190° (approx.)/0·5 mm. (see below). For analysis the *tetramine* was redistilled and the distillate filtered to remove traces of a waxy solid (Found: C, 40·5; H, 11·2; N, 46·8. $C_4H_{14}N_4$ requires C, 40·7; H, 11·9; N, 47·5%). The *tetrapicrate* was prepared in ethanol and formed a sticky precipitate which hardened gradually. Recrystallisation was best from water, though not entirely satisfactory since a small insoluble gummy residue always remained undissolved. Three recrystallisations gave a product (fine needles), m. p. 140° (with softening above 127°) (Found: C, 33·0; H, 2·8; N, 22·7. $C_{28}H_{26}O_{28}N_{16}$ requires C, 32·5; H, 2·5; N, 21·7%). The *tetrahydrochloride* crystallised on addition of excess of the concentrated acid to the tetramine, m. p. 270° (decomp.) (from ethanol—ether). (Found: C, 22·8; H, 4·2; N, 6·7; Cl, 63·4. $C_4H_9NCl_4$ requires C, 22·6; H, 4·2; N, 6·6; Cl, 66·6%).

Tosylation of High-boiling Amine from Ammonolysis of Tris(chloromethyl)aminomethane.—Tosylation by the Schotten–Baumann method with excess tosyl chloride, and acidification with hydrochloric acid, gave a gummy precipitate. The part insoluble in boiling methanol was recrystallised 5 times from glacial acetic acid, giving the *hexatosyl* derivative of the secondary amine corresponding to tetramine, small irregular plates, m. p. 275—278° (Found: C, 52·6; H, 5·4; N, 8·4; S, 16·6. $C_{50}H_{61}O_{12}N_7S_6$ requires C, 52·6; H, 5·3; N, 8·6; S, 16·8%).

Tris(carbethoxyaminomethyl)carbethoxyaminomethane.—(*a*) The tetramine (4·85 g.; 0·0411 mole) was dissolved in dilute sodium hydroxide (6·6 g. in 80 c.c. of water) and ethyl chloroformate (15·6 c.c.; 0·164 mole) added during ½ hour to the stirred solution at 0—10°. When about half of the ester had been added, a sticky solid made stirring difficult, and ether (100 c.c.) was added. The reaction was completed by 2½ hours' stirring at 0—10°; the suspension was then filtered and the solid washed with water. Yield 7·5 g. Evaporation of the ether layer of the filtrate gave a further small quantity of solid (1·2 g.). The total crude yield (52%) was recrystallised 3 times from 40% alcohol to give the pure *compound* as minute needles, m. p. 145—146° (Found: C, 47·4; H, 7·2; N, 13·4. $C_{16}H_{30}O_8N_4$ requires C, 47·3; H, 7·4; N, 13·8%).

(*b*) An attempt was made to improve the yield by simultaneously adding ethyl chloroformate and alkali (both in 28% excess) during 1 hour, the system being kept slightly alkaline throughout. The starting material was the tetramine disulphate, and sufficient alkali to liberate the free base was added before any addition of ethyl chloroformate. Addition of ether was again necessary to facilitate stirring. The whole of the reaction mixture was filtered to yield the crude product, m. p. 225—235° (with much previous softening). Crystallisation from acetic acid gave 5·6 g. of a white powder (E), m. p. 268° (decomp.), and concentration of the mother liquor, a sticky solid, m. p. 120—130° (washed with alcohol). Recrystallisation from 40% alcohol gave tris(carbethoxyaminomethyl)carbethoxyaminomethane (20%; m. p. 143—145°).

Recrystallised three times from acetic acid, (E) yielded minute needles of NN′-*bis*[*tri*(*carbethoxyaminomethyl*)*methyl*]*urea* (XIII), m. p. 272° (decomp.) (Found: C, 46·6; H, 7·2; N, 16·1. $C_{27}H_{50}O_{13}N_8$ requires C, 46·7; H, 7·2; N, 16·2%).

Attempted Preparation of Trisnitroaminomethylnitroaminomethane.—Triscarbethoxyaminomethylcarbethoxyaminomethane (5 g.) was added during 15 minutes to a stirred mixture of nitric acid (20 c.c.; *d* 1·52) and acetic anhydride (20 c.c.) at 0°, and stirring continued for a further 1½ hours. Pouring on ice gave a sticky gum which was washed with water until free from acid, but could not be crystallised. An attempt was made to hydrolyse the gum to the free tetranitroamine by heating it on a steam-bath with ammonia for 10 minutes. Acidification with concentrated hydrochloric acid gave no precipitate, and ether extraction gave ethyl carbamate, m. p. 48°, as the only crystalline product.

The gum from another nitration was dissolved in ether and ammonia gas passed in. A yellowish gum separated almost at once, and after decantation of the ether was dissolved in water and reprecipitated by hydrochloric acid. The product could not be crystallised, but dried to a hard, clear glass which did not give correct analyses for the tetranitroamine (Found: C, 29·1; H, 4·1; N, 26·2. Calc. for $C_4H_{10}O_8N_8$: C, 16·1; H, 3·4; N, 37·6%).

8-*Hydroxymethyl*-2 : 6-*dioxapyrrolizidine* (XIV).—(*a*) By the method of B.P. 564, 506, trishydroxymethylaminomethane (12·2 g.) was dissolved in 37% (w/w) formaldehyde (16·4 g.) and the solution evaporated at 30° under reduced pressure, giving the crude substance, m. p. 56—62° as colourless hygroscopic crystals.

(*b*) A mixture of trishydroxymethylaminomethane (20 g.), paraformaldehyde (10·2 g.), and benzene (75 c.c.) was refluxed in an apparatus fitted with a trap for collection of the azeotropically removed water. When the theoretical quantity (6 c.c.) had been collected (1½—2 hours) a small amount of solid was filtered off and the solution evaporated to yield the theoretical amount (24 g.) of non-hygroscopic product, m. p. 54—57°. Alternatively, the filtered benzene solution was allowed to crystallise giving very large crystals, m. p. 58—62°, and after removal of ¾ of the benzene from the mother liquors a further yield of less pure substance resulted. Total yield 88%.

Methiodide. The tertiary amine (2·06 g.) was dissolved in methanol (1 c.c.) and methyl iodide (1·75 c.c., *i.e.*, twice theory) was added. After 1 day the product (3·71 g.; 91·5%) was precipitated by addition of ether. Four recrystallisations from 96% alcohol gave the *methiodide*, m. p. 215° (decomp.) (Found: I, 46·6. $C_7H_{14}O_3NI$ requires I, 44·3%).

Acetyl derivative (XV). (*a*) 8-Hydroxymethyl-2 : 6-dioxapyrrolizidine was dissolved in a large excess of acetic anhydride containing 0·1% of sulphuric acid. After 1 day the excess of anhydride was decomposed by stirring with sodium acetate solution, and the product isolated by extraction with

chloroform. Recrystallisation of the crude product from ethanol–light petroleum gave the substance, m. p. 93—95°; yield 45%. The pure 8-*acetoxymethyl*-2 : 6-*dioxapyrrolizidine* (plates and needles), m. p. 94—95°, was obtained by recrystallisation in turn from ethanol–light petroleum, benzene, and ethanol (Found : C, 51·3; H, 6·7; N, 7·7. $C_8H_{13}O_4N$ requires C, 51·3; H, 7·0; N, 7·5%).

(*b*) Refluxing the hydroxy-compound for 2½ hours with a large excess of acetic anhydride gave the acetyl derivative, m. p. 89—93°. Yield 41%.

3-*Nitro*-4 : 4-*bisnitroxymethyloxazolidine* (XVI).—Finely powdered 8-hydroxymethyl-2 : 6-dioxapyrrolizidine (4 g.) was added gradually during 15—30 minutes to a stirred mixture of concentrated sulphuric acid (25 c.c.) and nitric acid (30 c.c.; *d* 1·52) at 0—5°. After a further 2 hours' stirring the mixture was poured on crushed ice and the crystalline precipitate collected, washed, and dried, giving the derivative, m. p. 67° (1·6 g., 22%). The pure *compound*, irregular plates, m. p. 67·5—70°, was obtained by 3 recrystallisations from methanol (Found : C, 22·7; H, 3·0; N, 21·1. $C_5H_8O_9N_4$ requires C, 22·4; H, 3·0; N, 20·9%).

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384. *Condensation of Nitromethane with Aldehydes. Derivatives of* 1-*Nitropent*-3-*en*-2-*ol.*

By Godfrey Fort and Andrew McLean.

Alkali-catalysed condensation of nitromethane with crotonaldehyde gave a poor yield of the unsaturated nitro-alcohol, 1-nitropent-3-en-2-ol, which on successive acetylation and dehydroacetylation yielded an unstable liquid, probably 1-nitropenta-1 : 3-diene. From 1-nitropent-3-en-2-ol, 1-benzamidopentan-2-one was prepared by successive hydrogenation, benzoylation, and chromic acid oxidation. Purification of 1-nitro-2-acetoxypent-3-ene by distillation yielded a residual substance which was not identified.

Although condensation of nitro-paraffins with aldehydes has been the subject of many publications, condensation with unsaturated aliphatic aldehydes was first described by Degering and Sprang (U.S.P. 2,332,482) while the present work was in progress. No yields are quoted by these authors but their results on the condensation of crotonaldehyde and nitromethane show general agreement with those reported in the present paper.

The main object of the present investigation was the preparation of 1-nitropenta-1 : 3-diene, a substance isomeric with the conjugated nitro-dienes previously prepared by Buckley and Charlish (*J.*, 1947, 1472) but differing from these in having the nitro-group in the terminal position. An unstable, though distillable, liquid, which was probably the required nitro-diene, was obtained by subjecting 1-nitropent-3-en-2-ol, the primary product of the alkali-catalysed condensation of nitromethane with crotonaldehyde, to successive acetylation with acetyl chloride and dehydroacetylation in presence of a catalytic amount of sodium acetate. The initial reaction of crotonaldehyde with nitromethane gave a maximum yield (on aldehyde) of about 40% and, with high molar ratios of nitromethane to aldehyde, there was evidence that the crotonaldehyde had reacted with more than one mol. of nitro-paraffin. No crystalline derivative for characterisation of the supposed nitro-diene could be obtained by the Diels–Alder reaction or otherwise, but a brittle polymer formed slowly at room temperature without catalyst and more rapidly in presence of sodium methoxide.

1-Nitropent-3-en-2-ol was reduced catalytically, giving poor yields of crude 1-aminopentan-2-ol. Oxidation of the N-*benzoyl* derivative of the latter gave 1-*benzamidopentan*-2-*one*.

Purification of 1-nitro-2-acetoxypent-3-ene by distillation gave a residue which yielded a *substance*, m. p. 102·5—103°, the structure of which was not determined but which was possibly a dimer of 1-nitropent-3-ene-2-ol.

Experimental.

1-*Nitropent*-3-*en*-2-ol.—Of a large number of condensations of nitromethane and crotonaldehyde carried out, the following are typical.

(*a*) Nitromethane (77 g.; 1·25 moles) was added gradually with stirring and cooling to a solution of potassium hydroxide (1·6 g.) in methanol (200 c.c.) followed by crotonaldehyde (70 g.; 1 mole) containing quinol (4 g.). During the addition of aldehyde (30 minutes) the temperature was kept below 30°. The reaction was completed by stirring for a further 25 minutes, the mixture acidified with concentrated hydrochloric acid, and the solution evaporated under reduced pressure (finally at 70°/15 mm.). Removal of potassium chloride by filtration gave a viscous, orange liquid (128 g.; theory 131 g.) which was divided into two parts. (i) 54 G. were distilled in nitrogen with addition of quinol (1 g.), giving nitropentenol (15·1 g.; 27%), b. p. 80°/3 mm.—110°/5 mm., as a yellow liquid; distillation was stopped when the bath temperature reached 170°, since at 190—200° violent decomposition was liable to occur (admission of air initiated violent decomposition at much lower temperatures). (ii) 74 G. were shaken with cold water (2000 c.c.). Three ether extractions of the filtered solution gave a golden liquid (42·7 g.) which on

distillation as in (i) gave nitropentenol (18·2 g.; 24%), b. p. 90°/2·5 mm.—110°/5 mm. For analysis a portion was redistilled (b. p. 91—100°/2 mm.) [Found: C, 45·2; H, 6·5; N, 10·0; *M* (cryoscopic in benzene), 133. Calc. for $C_5H_9O_3N$: C, 45·8; H, 6·9; N, 10·7%; *M*, 131].

(*b*) To a stirred solution of crotonaldehyde (105 g.; 1·5 moles) and quinol (6 g.) in methanol (300 c.c.) were added simultaneously nitromethane (91·5 g.; 1·5 moles) and sodium methoxide (0·62 g. sodium in 45 c.c. methanol). Sodium methoxide addition was rapid at first (30 c.c. in 3 minutes) and was complete in 16 minutes, while addition of nitromethane lasted 20 minutes during which the temperature was not permitted to rise above 30°. After reaction had been completed by continuing stirring for 20 minutes at 30°, the calculated amount of hydrochloric acid (2·67 c.c.; $d_4^{20°}$ 1·16) was added. Evaporation and filtration gave the crude product (150·2 g.; theory 196·5 g.) which was shaken with water and chloroform. The chloroform layer yielded a yellow liquid (133·7 g.) which, on distillation in nitrogen, gave two fractions: (i) b. p. 90—100°/2 mm. (64·5 g.; 32·8%); (ii) b. p. 100°/2 mm.—120°/10 mm. (27 g.). Redistillation of (ii) gave 12·9 g. (6·6%) of liquid (b. p. 91—100°/2 mm.). Yield of nitropentenol (b. p. 90—100°/2 mm.) 39·4%.

(*c*) Sodium methoxide (0·4 g. sodium in 40 c.c. methanol) was added with stirring and ice-cooling to a solution of nitromethane (91·5 g.; 1·5 moles) and quinol (0·05 g.) in methanol (50 c.c.). There was then added during 1½ hours at 1—5° with passage of nitrogen a solution of crotonaldehyde (17·5 g.; 0·25 mole) and quinol (0·05 g.) in methanol (20 c.c.). Thereafter, stirring was continued for 1 hour. Acidification with hydrochloric acid, filtration, and removal of methanol and excess of nitromethane below 50° in a stream of nitrogen gave crude nitropentenol (36·7 g.; theory 32·75 g.) which was taken up in chloroform. Washing, drying, and evaporation gave a liquid (27·4 g.) less viscous than the crude product in (*a*) and (*b*) above. Distillation up to a bath temp. of 190° in nitrogen into one receiver gave a distillate (23·1 g.) consisting of two main fractions, *viz.*, b. p. 80—95°/0·2 mm. and b. p. 170° (approx.)/0·7 mm. Redistillation of the whole in nitrogen gave nitropentenol (13·4 g.; 41% yield on aldehyde), b. p. 75—80°/0·3 mm. On further distillation a small fraction (1·0 g.), b. p. 80—115°/0·3—0·4 mm., was collected, but violent effervescence and tar formation prevented collection of the high-boiling fraction.

(*d*) A condensation was effected by using 3 times the theoretical quantity of nitromethane essentially under the conditions described in (*c*) but allowing the temperature to rise to 23°. On the basis of a small-scale (10 g.) distillation the yield of nitropentenol, b. p. 74°/0·1 mm.—90°/0·2 mm., was 43·5%, but on a larger scale (50 g.) was only 39%.

1-*Nitro*-2-*acetoxypent*-3-*ene*.—Interaction of 1-nitropent-3-en-2-ol and acetic anhydride and pyridine gave a tar, but reaction with acetyl chloride proceeded smoothly. (*a*) Crude undistilled nitropentenol (17·2 g.) prepared by method (*a*, ii) was treated with acetyl chloride (18·6 c.c.) at 30—35°. After evolution of hydrogen chloride had ceased the mixture was kept for 2 hours at room temperature, excess acetyl chloride distilled off, and chloroform added. The washed chloroform solution gave a pungent-smelling brown liquid (19·0 g.) which on distillation yielded 1-nitro-2-acetoxypent-3-ene (7·1 g.) as a colourless liquid, b. p. 97—103°/3—3·5 mm. [Violent decomposition at 200° (bath) prevented the distillation of higher-boiling fractions.] Yield 31·2% (on crude nitropentenol). Redistillation of 9·4 g. of the product in nitrogen gave a colourless liquid (6·6 g.) boiling at 96—101°/2 mm. but failing to give satisfactory analyses (Found: C, 47·2; H, 5·8; N, 8·9. Calc. for $C_7H_{11}O_4N$: C, 48·6; H, 6·4; N, 8·1%). (*b*) Distillation before acetylation gave less efficient conversion of crude nitropentenol into the acetyl derivative. To distilled nitropentenol (4·8 g.) acetyl chloride (10·4 c.c.; 4 times theory) was added gradually with cooling below 35°. The product was isolated as described above. The crude acetyl compound (4·2 g.) gave, on distillation, 3·5 g., b. p. 104—115°/5 mm. Yield 55% (on distilled nitropentenol).

1-*Nitro*-2-(3 : 5-*dinitrobenzoxy*)*pent*-3-*ene*.—This was prepared by heating the nitro-alcohol with 3 : 5-dinitrobenzoyl chloride until hydrogen chloride evolution ceased, and recrystallising the product twice from ethanol–light petroleum and once from aqueous methanol. The *compound* (needles) melted at 75·5—77° (Found: C, 43·3; H, 2·02; N, 12·5. $C_{12}H_{11}O_8N_3$ requires C, 44·3; H, 3·4; N, 12·9%).

1-*Nitropenta*-1 : 3-*diene*.—(*a*) Powdered anhydrous sodium acetate (0·3 g.) and quinol (0·2 g.) were added to 1-nitro-2-acetoxypent-3-ene (13·0 g.) and the mixture distilled in a stream of nitrogen. Three fractions were collected: (i) <130° (bath)/10 mm., (ii) 84—94°/9 mm. (6·2 g.), and (iii) 85—90°/5 mm. (1·8 g.). Fraction (i) was largely acetic acid, and (ii) was a highly refractive yellow liquid of penetrating odour consisting of crude nitropentadiene (yield 73%).

(*b*) In another preparation the acetic acid and nitropentadiene were collected as one fraction and the former removed by addition of chloroform and washing in turn with water and sodium hydrogen carbonate. Fractionation gave a product boiling at 85—100°/5—8 mm., yielding on redistillation nitropentadiene, b. p. 88—90°/8 mm. A sample of the substance was analysed but, in absence of quinol, it had decomposed appreciably before the analysis could be completed (Found: C, 51·3; H, 6·2; N, 10·4. Calc. for $C_5H_7O_2N$: C, 53·1; H, 6·2; N, 12·4%). On standing at room temperature 1-nitropenta-1 : 3-diene formed a brittle, amber resin in a few days, or, in presence of quinol, in a few weeks. Polymerisation was catalysed by sodium methoxide. A solution of nitropentadiene (2·17 g.) in dioxan (5·7 c.c.) was cooled in ice, and sodium methoxide (0·025 g. of sodium in 1·5 c.c. methanol) was added during 2 minutes with stirring at 0°. After being stirred for 1 hour at room temperature the mixture was poured into dilute acetic acid. The precipitated gum which still contained some monomer was washed repeatedly with water and dried in a vacuum desiccator (yield 0·84 g.; 39%). The product was almost completely soluble in acetone.

Attempted Cyanoethylation of 1-*Nitropent*-3-*en*-2-*ol*.—The method was essentially that of Bruson and Riener (*J. Amer. Chem. Soc.*, 1943, **65**, 23). The nitro-alcohol (15 g.) was dissolved in dioxan (30 c.c.) and Triton B (40% aqueous benzyltrimethylammonium hydroxide; 2 g.) was added, followed during 40 minutes below 28° by acrylonitrile (18·2 g.; 3 mols.). After 6 hours at room temperature the product was isolated by extraction with chloroform and crystallised partly on addition of methanol (1·7 g.; washed with methanol). Tris-2-cyanoethylnitromethane was recrystallised thrice from methanol and formed needles, m. p. 112·5—113° (Found: C, 54·8; H, 5·4; N, 24·4. Calc. for $C_{10}H_{12}O_2N_4$: C, 54·6; H, 5·5; N, 25·4%).

Crystalline Substance from Purification of 1-*Nitro*-2-*acetoxypent*-3-*ene*.—Crude distilled acetyl compound [b. p. <150° (bath)/3 mm.] was redistilled up to 105—110°/3 mm. (bath 150°). The dark, viscous residual liquid crystallised to a small extent on standing. (Redistillation of the twice distilled acetyl compound gave a further, small, partly crystalline residue, so that the crystalline *substance* was apparently derived from the acetyl compound.) The viscous mother liquor was removed and the crystals washed and recrystallised; m. p. 98·5—100·5° (from methanol). From several hundred g. of crude acetyl compound about 10 g. of crystals were obtained. Five more recrystallisations from ethanol raised the m. p. to 102·5—103°, and from benzene this was unaltered [Found (averages of 3 determinations): C, 45·9; H, 6·9; N, 10·2; *M* (Rast), 230—400. $(C_5H_9O_3N)_n$ requires C, 45·8; H, 6·9; N, 10·7%]. The following qualitative results were obtained. (*a*) Tests with bromine in chloroform and permanganate in acetone revealed no unsaturation. (*b*) The substance was recovered unchanged after attempted dehydroacetylation by refluxing it with sodium acetate in acetic acid or with potassium hydrogen carbonate in benzene. (*c*) After treatment for 4 days at room temperature with benzoyl chloride (50% excess on basis of one HO-group per $C_5H_9O_3N$ unit) in pyridine, 64% of starting material was recovered. (*d*) After treatment for 4 days at room temperature and 1 hour at 45° in acetic acid with chromium trioxide (75% excess on basis of one HO-group per $C_5H_9O_3N$ unit), 43% of the starting material was recovered unchanged. (*e*) The substance was recovered after being shaken for 6 hours at room temperature with hydrogen and platinum dioxide in acetic acid–acetic anhydride. With a large quantity of palladium black (prepared by method of Heilbron, Sexton, and Spring, *J.*, 1929, 929) in ethanol at room temperature, absorption of hydrogen ceased after 8 hours and was approximately that calculated for reduction of one nitro-group per $C_5H_9O_3N$ unit. The product was a strongly basic liquid with an odour resembling that of 1-aminopentan-2-ol (see below), and gave a picrate, m. p. 265—270° (decomp.), after recrystallisation from ethanol–ether. With benzoyl chloride in pyridine and with nitrourea the crude base gave non-crystalline products.

1-*Aminopentan*-2-*ol*.—1-Nitropent-3-en-2-ol (13·4 g.; b. p. 75—80°/0·3 mm.) in ethanol (200 c.c.) was hydrogenated at 80 atmospheres (initial pressure) for 5 hours at 35—40°, using Raney nickel catalyst (3 g.). Charcoal treatment and evaporation gave a brown syrup (7·15 g.; theory 10·5 g.), which, on distillation, yielded a pale-yellow liquid (3·98 g.; 38%), b. p. 75° (approx.)/3·5 mm.; a redistilled sample, b. p. 75—80°/3·5—4 mm., gave unsatisfactory analyses (Found: C, 56·0; H, 10·0; N, 12·0. Calc. for $C_5H_{13}ON$: C, 58·2; H, 12·6; N, 13·6%). Interaction of the base and picric acid gave a tar, and nitrourea gave fibrous needles, m. p. 240° (decomp.) which were not the derived urea.

1-*Benzamidopentan*-2-*ol*.—Benzoyl chloride (1 mole) was added gradually during 1½ hours to a stirred suspension of sodium carbonate in a benzene solution of the amino-alcohol (1 mole) at 10°, and the mixture stirred until all benzoyl chloride had reacted (4 hours). Hot filtration and cooling gave plates (56% yield), m. p. 111—113°. Concentration of the benzene mother liquor and addition of light petroleum gave a further small quantity of crystals (total yield 61%). Recrystallised twice from benzene the *compound* melted at 112—113·5° (Found: C, 69·6; H, 8·1; N, 7·5. $C_{12}H_{17}O_2N$ requires C, 69·5; H, 8·2; N, 6·8%).

1-*Benzamidopentan*-2-*one*.—1-Benzamidopentan-2-ol (3·10 g.) in acetic acid (20 c.c.) was added to a solution of chromium trioxide (1·05 g.) in water (2 c.c.). After 2 days at room temperature and 1 hour at 45° a semi-crystalline product was isolated by ether extraction. Addition of benzene and filtration gave unchanged 1-benzamidopentan-2-ol. The benzene solution on concentration gave a semi-crystalline, sticky mass, which, on prolonged filtration, yielded crystals, m. p. *ca.* 55°. Four recrystallisations from light petroleum (b. p. 40—60°) gave the *compound* as plates, m. p. 61·5—62·5 (Found: C, 70·3; H, 7·3; N, 6·8. $C_{12}H_{15}O_2N$ requires C, 70·3; H, 7·3; N, 6·8%).

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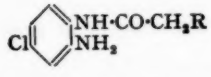
385. *Structure and Antimalarial Activity. Part III. Some Benziminazoles.*

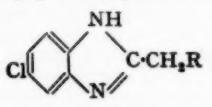
By D. Muriel Hall and E. E. Turner.

5(or 6)-*Chloro*-2-*diethylamino*- and 5(or 6)-*chloro*-2-*piperidino-methylbenziminazoles* have been prepared by ring-closure of the corresponding o-*aminoacetanilides*. Cyclisation of p-*chloro*-o-*amino*-β-*piperidinobutyranilide* gave only the unsaturated 5(or 6)-*chloro*-2-*propenylbenziminazole* by elimination of piperidine.

In Parts I and II (*J.*, 1945, 694, 699) a number of basic derivatives of various heterocyclic systems was described. The investigation has now been extended to the benziminazole series.

p-*Chloro*-o-*nitro*-ω-*chloroacetanilide* was heated with diethylamine or piperidine under pressure and the resulting p-*chloro*-o-*nitro*-ω-*diethylamino*(or *piperidino*)*acetanilide* reduced to

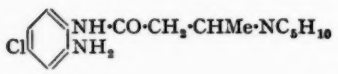
(I.) 

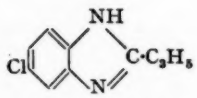
 (II.)

the o-*amino*-compound (I; R = NEt_2 or NC_5H_{10}). The latter readily underwent ring closure in boiling glacial acetic acid solution in the presence of sodium acetate to give 5(or 6)-*chloro*-2-

diethylamino(or *piperidino*)*methylbenziminazole* (II; R = NEt_2 or NC_5H_{10}). The *hydrochlorides* of (I) and (II) showed no antimalarial activity when tested against *Plasmodium relictum* and *P. gallinaceum*.

p-*Chloro*-o-*nitro*-β-*bromobutyranilide* reacted with piperidine at 120° to give a mixture of *p*-chloro-*o*-nitroaniline, p-*chloro*-o-*nitrocrotonanilide* and p-*chloro*-o-*nitro*-β-*piperidinobutyranilide*. In a subsequent preparation with only a slight change in the experimental conditions no unsaturated compound was formed, but the crotonanilide was formed slowly by the elimination of piperidine from the butyranilide when the latter was heated at 120°. Catalytic hydrogenation of *p*-chloro-*o*-nitro-β-piperidinobutyranilide gave the o-*amino*-compound (III) with some *azoxy*-5-*chloro*-2-β-*piperidinobutyramidobenzene*. Attempted ring closure of (III) in boiling glacial acetic acid containing sodium acetate gave a resin but, at the higher temperature made possible by using propionic acid and sodium propionate and boiling for not more than 10 minutes, unpolymerised 5(or 6)-*chloro*-2-*propenylbenziminazole* (IV) was obtained. It was not found

(III.) 



(IV.)

possible to induce ring closure without the elimination of piperidine. In (IV) C_3H_5 is either $\cdot CH{:}CH\cdot CH_3$ or $\cdot CH_2\cdot CH{:}CH_2$, the former being preferred on grounds of conjugative stabilisation.

Ahmed, Narang, and Ray (*J. Indian Chem. Soc.*, 1938, **15**, 152) prepared 2-diethylaminomethyl- and 2-piperidinomethyl-benziminazole but in attempts to prepare the corresponding ethyl compounds they obtained only a polymer of 2-vinylbenziminazole.

The pharmacological tests were done by Dr. Ann Bishop of the Molteno Institute and Miss I. Tonkin of the National Institute for Medical Research.

Experimental.

p-*Chloro*-o-*nitro*-ω-*chloroacetanilide*.—(For the nitration of *p*-chloroacetanilide see *J.*, 1945, 699.) Chloroacetyl chloride (50 g.) was added to *p*-chloro-*o*-nitroaniline (50 g.) in the presence of dry benzene, and the mixture heated under reflux for 1 hour. p-*Chloro*-o-*nitro*-ω-*chloroacetanilide* crystallised from the cooled benzene solution in yellow needles, m. p. 141—142° (Found: Cl, 28·6. $C_8H_6O_3N_2Cl_2$ requires Cl, 28·5%); yield, 69·5 g., 97%.

p-*Chloro*-o-*nitro*-ω-*diethylaminoacetanilide*.—*p*-Chloro-*o*-nitro-ω-chloroacetanilide (25 g., 1 mol.) and diethylamine (16·5 g., 2·2 mols.) were heated together in benzene solution for 3 hours on a water-bath. Diethylamine hydrochloride was filtered off, and the benzene solution evaporated. The residue contained a considerable amount of unchanged chloro-compound which could not be removed by fractional crystallisation; the fractions were therefore collected and heated in a sealed tube with excess of diethylamine for 5 hours in a bath kept at 112°. The product was poured into water and p-*chloro*-o-*nitro*-ω-*diethylaminoacetanilide* separated as an oil which soon solidified, and crystallised from alcohol in light yellow needles, m. p. 58—59° (Found: N, 14·7. $C_{12}H_{16}O_3N_3Cl$ requires N, 14·7%). Traces of unchanged chloro-compound were removed by dissolving the base in dilute hydrochloric acid, filtering, and reprecipitating with ammonia.

p-*Chloro*-o-*amino*-ω-*diethylaminoacetanilide*.—Reduction of the above nitro-compound (10 g.) in alcoholic solution with hydrogen in the presence of Raney nickel catalyst gave p-*chloro*-o-*amino*-ω-*diethylaminoacetanilide*, which crystallised from light petroleum (b. p. 80—100°) in flat rods, m. p. 75—76° (Found: N, 16·9. $C_{12}H_{18}ON_3Cl$ requires N, 16·4%); yield, 7·7 g., 86%. The *dihydrochloride* was obtained by passing hydrogen chloride into a solution of the base in dry benzene. It crystallised from alcohol–light petroleum (b. p. 40—60°) in fine needles, m. p. 188° (decomp.) (Found: N, 12·4. $C_{12}H_{20}ON_3Cl_3$ requires N, 12·8%).

5(or 6)-*Chloro*-2-*diethylaminomethylbenziminazole*.—*p*-Chloro-*o*-amino-ω-diethylaminoacetanilide (3·3 g.) and fused sodium acetate (2 g., 2 mols.) in glacial acetic acid (15 c.c.) were heated at the boiling point for 1 hour. The cooled solution was made alkaline with 10% sodium hydroxide solution and extracted with benzene. The benzene solution was dried (K_2CO_3) and evaporated, giving a residue of 2·5 g. (80%) of 5(or 6)-*chloro*-2-*diethylaminomethylbenziminazole*, which crystallised from light petroleum (b. p. 80—100°) in needles, m. p. 150—151° (Found: N, 17·9. $C_{12}H_{16}N_3Cl$ requires N, 17·7%). The *dihydrochloride* was obtained by passing hydrogen chloride into a solution of the benziminazole in dry benzene. It crystallised from alcohol–light petroleum (b. p. 40—60°) in prisms, m. p. indefinite (Found: N, 13·55. $C_{12}H_{15}N_3Cl_3$ requires N, 13·5%).

p-*Chloro*-o-*nitro*-ω-*piperidinoacetanilide*.—*p*-Chloro-*o*-nitro-ω-chloroacetanilide (20 g., 1 mol.) and piperidine (13·6 g., 2 mols.) were heated in a bath kept at 140° for 4 hours. The product was cooled, ground with water, and crystallised from alcohol; yield of p-*chloro*-o-*nitro*-ω-*piperidinoacetanilide* 18 g., 75%; pale yellow needles, m. p. 99°, from alcohol or light petroleum (b. p. 80—100°) (Found: N, 13·8. $C_{13}H_{16}O_3N_3Cl$ requires N, 14·1%).

p-*Chloro*-o-*amino*-ω-*piperidinoacetanilide*.—The above nitro-compound (18 g.) was reduced in alcoholic solution with hydrogen in the presence of Raney nickel catalyst. p-*Chloro*-o-*amino*-ω-*piperidinoacetanilide* separated after evaporation of most of the alcohol; yield 13·5 g., 83%. It crystallised from slightly aqueous alcohol in almost colourless, thin plates, m. p. 121—122·5° (Found:

N, 15·7. $C_{13}H_{16}ON_3Cl$ requires N, 15·7%). The *monohydrochloride* was obtained by passing hydrogen chloride into a solution of the base in acetone. It crystallised from alcohol in plates, m. p. 217° (decomp.) (Found : N, 13·5. $C_{13}H_{19}ON_3Cl_2$ requires N, 13·8%).

5(or 6)-*Chloro*-2-*piperidinomethylbenziminazole*.—*p*-Chloro-*o*-amino-ω-piperidinoacetanilide (6·5 g.) and fused sodium acetate (4 g., 2 mols.) in glacial acetic acid (30 c.c.) were heated at the boiling point for 1 hour. 5(or 6)-*Chloro*-2-*piperidinomethylbenziminazole* was precipitated from the solution by 10% sodium hydroxide solution, and crystallised from light petroleum (b. p. 100—120°) in plates, m. p. 163—164° (Found : N, 16·9. $C_{13}H_{16}N_3Cl$ requires N, 16·8%); yield 5 g. (82%). The *monohydrochloride*, obtained by passing hydrogen chloride into a solution of the benziminazole in acetone, crystallised from alcohol in needles, m. p. 249—251° (decomp.) (Found : N, 14·1. $C_{13}H_{17}N_3Cl$ requires N, 14·7%).

β-*Bromobutyryl Chloride*.—β-Bromobutyric acid (87 g.) was added to thionyl chloride (79 g.) with cooling, and the mixture heated for 2 hours on a water-bath. The product was distilled under reduced pressure; yield 81 g., 83%; b. p. 61°/16 mm.

p-*Chloro*-o-*nitro*-β-*bromobutyranilide*.—β-Bromobutyryl chloride (16 g.) was added to *p*-chloro-*o*-nitroaniline (10 g.) in the presence of dry benzene (about 50 c.c.), and the mixture heated under reflux for 1 hour. p-*Chloro*-o-*nitro*-β-*bromobutyranilide* crystallised from the benzene solution on cooling and was recrystallised from alcohol; yield 16 g., 86%; yellow flat needles, m. p. 99° (Found : 5·148 mg. gave 5·250 mg. of AgCl + AgBr. $C_{10}H_{10}O_3N_2ClBr$ requires 5·300 mg.). (It resembles 5-chloroacridine in its irritant action on the skin.)

p-*Chloro*-o-*nitro*-β-*piperidinobutyranilide*.—(a) *p*-Chloro-*o*-nitro-β-bromobutyranilide (20 g.) and piperidine (12 g., 2·2 mols.) were heated for 5 hours in a bath kept at 120°. The product was poured into water and, when the gum had become solid, treated with dilute hydrochloric acid. The insoluble residue was crystallised from aqueous alcohol giving *ca.* 2 g. of *p*-chloro-*o*-nitroaniline, m. p. and mixed m. p. 116°. The acid solution on treatment with ammonia gave a yellow solid, which after crystallisation from aqueous alcohol still had an indefinite m. p. Repeated fractional crystallisations from light petroleum gave (1) a little more *p*-chloro-*o*-nitroaniline, m. p. 115—117°; (2) p-*chloro*-o-*nitrocrotonanilide*, brown-yellow, flat rods, m. p. 157—158°, from light petroleum (b. p. 80—100°) (Found : C, 50·0; H, 3·8; N, 11·65. $C_{10}H_9O_3N_2Cl$ requires C, 49·9; H, 3·8; N, 11·65%); (3) p-*chloro*-o-*nitro*-β-*piperidinobutyranilide*, yellow rods, m. p. 65—66°, from light petroleum (b. p. 60—80°) (Found : C, 55·1; H, 6·2; N, 12·65. $C_{15}H_{20}O_3N_3Cl$ requires C, 55·3; H, 6·2; N, 12·9%).

(b) *p*-Chloro-*o*-nitro-β-bromobutyranilide (32 g.) and piperidine (19 g.) were heated for 3 hours in a bath kept at 125°. The product was dissolved in benzene, and washed with water and then with dilute hydrochloric acid. Evaporation of the benzene solution gave *ca.* 3 g. of *p*-chloro-*o*-nitroaniline, m. p. 114—116°. The acid solution was treated with ammonia, and the precipitate crystallised from light petroleum (b. p. 60—80°); yield of *p*-chloro-*o*-nitro-β-piperidinobutyranilide, m. p. 63—65°, 19 g., 58%. In this experiment no *p*-chloro-*o*-nitrocrotonanilide could be detected.

p-*Chloro*-o-*amino*-β-*piperidinobutyranilide*.—*p*-Chloro-*o*-nitro-β-piperidinobutyranilide (6·5 g.) was reduced in alcoholic solution with hydrogen in the presence of Raney nickel catalyst. During the reduction the product separated as a white solid; this was redissolved with hot alcohol, and the nickel filtered from the hot solution. p-*Chloro*-o-*amino*-β-*piperidinobutyranilide* crystallised from the solution after evaporation of most of the alcohol. It was readily soluble in hot alcohol or hot benzene but sparingly soluble in the cold. It crystallised from benzene in needles, m. p. 141·5° (Found : C, 60·8; H, 7·2; N, 14·2. $C_{15}H_{22}ON_3Cl$ requires C, 60·9; H, 7·5; N, 14·2%); yield 2·5 g., 42%. The amine was readily soluble in the cold in a mixture of piperidine and alcohol, but it was not possible to carry out the reduction in this solvent since piperidine poisoned the catalyst.

The reduction was repeated on 10·5 g. of the nitro-compound and, after filtration of the nickel, hot water was added to the hot alcoholic solution. On cooling, yellow crystals (3·5 g.; 18%) were deposited. This substance crystallised from light petroleum (b. p. 100—120°) in yellow rectangular prisms, m. p. 156—157°, and proved to be *azoxy*-5-*chloro*-2-β-*piperidinobutyramidobenzene* (Found : C, 59·6; H, 6·7; N, 13·7. $C_{30}H_{40}O_3N_6Cl_2$ requires C, 59·7; H, 6·7; N, 13·9%). The mother-liquors after removal of the azoxy-compound were treated with more water and extracted with chloroform. Evaporation of the chloroform gave a residue which on crystallisation from benzene yielded 1·4 g. (15%) of the normal amine, m. p. 141·5°.

Benziminazole Formation from p-*Chloro*-o-*amino*-β-*piperidinobutyranilide*.—(1) The amine (0·5 g.) with fused sodium acetate (0·3 g.) in glacial acetic acid (3 c.c.) was heated at the boiling point for 45 mins. A gum separated which was insoluble in water, and more gum was precipitated on addition of 10% sodium hydroxide solution. The gum was readily soluble in alcohol and benzene but would not crystallise. It was presumably polymerised 5(or 6)-chloro-2-propenylbenziminazole (cf. Ahmed, Narang, and Ray, *loc. cit.*).

(2) The above amine (0·5 g.) with fused sodium propionate (0·32 g.) in propionic acid (5 c.c.) was heated at the boiling point for 10 mins. Dilute sodium hydroxide solution was added, and the precipitate (0·3 g., 90%) crystallised from benzene. 5(or 6)-*Chloro*-2-*propenylbenziminazole* was obtained as a white microcrystalline powder, m. p. 184—187° (Found : C, 62·5; H, 4·7; N, 14·8. $C_{10}H_9N_2Cl$ requires C, 62·3; H, 4·7; N, 14·6%).

Microanalyses are by Drs. Weiler and Strauss, Oxford.

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UNIVERSITY OF LONDON (BEDFORD COLLEGE). [*Received, January 10th*, 1948.]

386. *Researches on Ammines. Part X. Triammines of Bivalent Platinum.*

By Herbert J. S. King.

There are shown to be two classes of platinous triammines. The one class, which includes the chloro-, bromo-, and nitro-triamminoplatinous salts, dissolve in water as such, and are shown by conductivity measurements to behave as salts of univalent kations. Solutions of these compounds also yield *pink* chloroplatinites and acido-triammine picrates. The other class dissolve with complete or substantial conversion into aquo-triammines: $[Pt(NH_3)_3X]X + H_2O = [Pt(NH_3)_3(H_2O)]X_2$. The nitrato-, sulphato-, and picrato-triammines undergo complete aquation, and conductivity measurements indicate the presence of salts of bivalent kations. Solutions of these salts yield aquotriammino-platinous chloroplatinite and picrate, the former being green. Conversion into aquo-salt is partial in the cases of carbonato- and oxalato-triammines.

In $[Pt(NH_3)_3(H_2N\cdot CH_2\cdot CH_2\cdot NH_2)]Cl_2$ the ethylenediamine molecule is shown to be attached to platinum at one point only, so that the platinous atom is still 4-covalent. If one molecule of ammonia is expelled, the ethylenediamine molecule occupies *two* positions in the complex. It is concluded that bivalent platinum has no tendency to exist in the 5-covalent state.

The acidotriamminoplatinous salts are of particular interest since they constitute the only group of metallic ammines hitherto investigated in which an acid radical forms part of a 4-covalent kation. The existence of two classes of platinous diacido-diammines was demonstrated in Part IX (*J.*, 1938, 1338). Members of the one class, which includes the dichloro-, dinitro-, di-iodo-, and dihydroxo-compounds, dissolve in water unchanged, while the other class, to which the dinitrato-, dipicrato-, and sulphato-diammines belong, dissolve as diaquo-salts, which, however, exist only in solution: $[Pt(NH_3)_2X_2] + 2H_2O \rightleftharpoons [Pt(NH_3)_2(H_2O)_2]X_2$. It has now been shown that there are similarly two types of platinous acido-triammines. In aqueous solution, the equilibrium $[Pt(NH_3)_3X]Y + H_2O \rightleftharpoons [Pt(NH_3)_3(H_2O)]XY$ lies almost entirely to the left in the one case and to the right in the other, the behaviour depending on the nature of X. In the former case, the solutions are neutral, while in the latter they contain aquotriammino-platinous salts, the noticeable acidity of which (less pronounced, however, than that of the corresponding diammines) is due to the hydroxo-aquo-equilibrium: $[Pt(NH_3)_3(H_2O)]X_2 \rightleftharpoons [Pt(NH_3)_3(OH)]X + HX$.

The aquotriammine salts, like the diaquodiammines, usually exist only in solution, the solid compounds which separate from the solutions being the original acidotriammines. The solutions containing acido-triammines give, with a soluble chloroplatinite, pink precipitates of the corresponding chloroplatinites, while those containing aquo-triammines yield a green precipitate of aquotriamminoplatinous chloroplatinite. The two classes also react differently with ammonium picrate, the former reacting with one mol. of picrate to form an acidotriammino-platinous picrate while the latter yield picratotriamminoplatinous picrate with two mols. of picrate. Evidently aquotriamminoplatinous picrate is unstable in the solid state but is present in the aqueous solution of the picrato-picrate (see Table II).

That chloro-, bromo-, and nitro-triamminoplatinous salts dissolve without aquation has been demonstrated by measurement of their electrical conductivities, which are of the order required for salts of univalent kations (see Table I). This conclusion was confirmed by precipitation of pink chloroplatinites and preparation of *chloro-*, *bromo-*, and *nitro-triamminoplatinous picrates*.

The only information available regarding other acidotriamminoplatinous salts is due to Cleve (*K. Svensk Vet. Akad. Handl.*, 1872, **10**, No. 9), who claimed to have obtained the nitrate $Pt(NH_3)_3(NO_3)_2$ and the sulphate $Pt(NH_3)_3SO_4$ by interaction of chlorotriamminoplatinous chloroplatinite (Cleve's salt) and silver nitrate or sulphate. No details were recorded, and attempts to prepare the salts by this method have proved unsuccessful. Two equivalents of silver salt should react with one molecular proportion of Cleve's salt yielding *chlorotriammino-platinous nitrate* or sulphate, and this has been verified experimentally in the case of the former salt. When, however, four equivalents of silver salt were used, as required by the equation $[(Pt(NH_3)_3Cl]_2PtCl_4 + 4AgNO_3 = 2[(Pt(NH_3)_3(NO_3)]NO_3 + 2AgCl + Ag_2PtCl_4$, the filtrate was not chlorine-free, and this was found to be due to interaction between silver chloroplatinite and silver nitrate (see p. 1914). It was found possible to isolate *nitratotriamminoplatinous nitrate* by carrying out Cleve's preparation in two stages, treating chlorotriamminoplatinous nitrate, prepared as above, with one mol. of silver nitrate, but the compound was more conveniently prepared by treating chlorotriamminoplatinous chloride with silver nitrate. The product is hemi-hydrated so formulation as an aquo-salt is excluded. It dissolved easily in water and the noticeable acidity of the solution suggested that the salt was present in solution, not as

nitratotriammino-, but as aquotriammino-platinous nitrate. This conclusion was confirmed (*a*) by preparation from it of aquotriamminoplatinous chloroplatinite (green) and *picratotriamminoplatinous picrate*, (*b*) by measurement of the electrical conductivity of the solution, which was of the order required for a salt of a bivalent kation (see Table II).

The *sulphato-triammine* was prepared by treating a solution containing aquotriammino-platinous nitrate with excess of sulphuric acid. The product, after drying over phosphoric oxide, contained only half the amount of water required for aquotriamminoplatinous sulphate. It could be formulated alternatively as (I) or (II), the sulphate radical in (II) being attached to

(I.) (II.)

the platinum atom at one point only. A compound of formula (II) would be analogous to the sulphatopentamminocobaltic salts (Jörgensen, *J. pr. Chem.*, 1885, **31**, 262), containing a " bound " sulphate ion, and would be a non-electrolyte if it dissolved without aquation. The aqueous solution, however, was acid to litmus and yielded green aquotriamminoplatinous chloroplatinite when treated with a soluble chloroplatinite. Thus solution had been accompanied by aquation, which might be expected to yield aquotriamminoplatinous sulphate, $[Pt(NH_3)_3(H_2O)]SO_4$, whichever formula is adopted for the solid substance. The ease with which aquation occurs favours formula (II). The presence in solution of the aquotriammine salt was confirmed by conductivity measurements (Table II).

Carbonato- and *oxalato-triamminoplatinum* have been obtained by the action of excess of silver carbonate or oxalate on *bromotriamminoplatinous bromide*, and in these cases also formulation of the solid compounds as aquo-salts is excluded, since the former is hemi-hydrated and the latter can be obtained anhydrous. They may be formulated analogously to formulæ (I) and (II) given for the sulphato-triammine. However, it seems unlikely, in view of the strong tendency of the carbonate and the oxalate radical to complex formation, that compounds of structure (I) would undergo aquation. Actually, sufficient aquation occurs for the salts to yield green precipitates with the chloroplatinite ion, though the conductivity data show that this aquation is very incomplete compared with that of the sulphato-triammine. The conductivity data for the oxalato-triammine are so low that formula (I) is definitely excluded.

It has frequently been suggested that in the process of ammine formation, the metals tend to simulate the electronic arrangement of the next inert gas. In the case of the bivalent platinum ion, this would require quinquecovalency (2, 8, 18, 32, 16 ⟶ 2, 8, 18, 32, 18, 8). As no well-established examples of quinquecovalent platinum have hitherto been described, an attempt was made to prepare such a compound by treating chlorotriamminoplatinous chloride with ethylenediamine. It might be expected that the powerful chelate group present in the molecule of this substance would attach itself directly to the complex, if 5-covalency is possible, yielding ethylenediaminotriamminoplatinous chloride $[Pt(NH_3)_3en]Cl_2$ (where en = $NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$). A *compound* of this molecular formula has actually been obtained, but it reacted with three molecular proportions of ammonium picrate, yielding

$$[Pt(NH_3)_3\{en\ H\ (C_6H_2O_7N_3)\}](C_6H_2O_7N_3)_2.$$

Thus the ethylenediamine molecule is attached to the platinum atom at one point only, and the platinum is still in the 4-covalent state. When $[Pt(NH_3)_3en]Cl_2$ was titrated with acid or boiled with water, a molecule of ammonia was removed, and the ethylenediamine molecule then occupied two positions in the complex, as was shown by precipitation of $[Pt(NH_3)_2en](C_6H_2O_7N_3)_2$ by *excess* of picrate. These results indicate that there is no tendency for bivalent platinum to exist in the 5-covalent state.

Experimental.

Chlorotriamminoplatinous Chloride.—Using Tschugaev's method (*J.*, 1915, **107**, 1249), difficulty was experienced in obtaining the compound pure. The following modification gave excellent results. 3·5 G. of tetramminoplatinous chloride were boiled for 3 minutes with 9·66 g. of Cleve's salt (8% excess) and 350 ml. of water acidified with hydrochloric acid. After cooling, the green Magnus salt and excess of Cleve's salt were removed and the filtrate was concentrated to small bulk at 50° under reduced pressure. After further filtration from traces of Cleve's salt, the remaining water was removed in a vacuum over sulphuric acid, and the solid product left over soda–lime to remove traces of hydrogen chloride (yield 6·1 g.). If less water or smaller excess of Cleve's salt was used, the product was contaminated with tetrammine.

Chlorotriamminoplatinous Nitrate.—3 G. of Cleve's salt were heated to 70° with 1·132 g. (2 mols.) of silver nitrate and 120 ml. of water. After collection of silver chloroplatinite, the colourless filtrate was concentrated to 30 ml. under reduced pressure at 50°. On addition of alcohol and ether, white, irregular, microscopic plates separated (0·57 g.) (Found : Pt, 56·7; N, 16·5; Cl, 10·0. $[Pt(NH_3)_3Cl]NO_3$ requires

Pt, 56·8; N, 16·3; Cl, 10·3%). The *compound* was easily soluble, giving a neutral solution which gave no immediate precipitate with silver nitrate. The silver chloroplatinite was suspended in water and left overnight in contact with a further 2 mols. of silver nitrate. The filtrate from silver chloride and unchanged chloroplatinite contained only 0·32 mol. of silver nitrate. Chlorotriamminoplatinous nitrate was best prepared by adding 0·5355 g. (1 mol.) of silver nitrate dropwise to a solution of chlorotriamminoplatinous chloride (1 g.). The filtrate was evaporated in a vacuum over sulphuric acid, yielding 0·95 g. of square plates (Found: Pt, 56·6; Cl, 10·2%). The aqueous solution gave a pink precipitate with ammonium chloroplatinite.

Chlorotriamminoplatinous picrate was precipitated as large yellow needles (1·5 g.) on mixing solutions of chlorotriamminoplatinous chloride (1 g.) and ammonium picrate (1·2 mols.) {Found: Pt, 38·4; N, 16·3; Cl, 6·7. $[Pt(NH_3)_3Cl](C_6H_2O_7N_3)$ requires Pt, 38·3; N, 16·5; Cl, 7·0%}.

Bromotriamminoplatinous bromide does not appear to have been isolated previously, though Tschugaev (*loc. cit.*) obtained the bromoplatinite $[Pt(NH_3)_3Br]_2PtBr_4$. The salt has now been prepared by converting chlorotriamminoplatinous chloride (2 g.) into aquotriamminoplatinous nitrate in 20 ml. of water (see nitratotriamminoplatinous nitrate below). The ice-cooled product was treated with colourless fuming hydrobromic acid (20 ml.), whereupon an immediate cream precipitate was obtained (1·8 g. of microscopic, acicular aggregates). It was washed successively with alcohol and ether and dried over soda–lime (Found: Pt, 48·2; N, 10·2; Br, 39·4. $[Pt(NH_3)_3Br]Br$ requires Pt, 48·1; N, 10·3; Br, 39·4%). 0·636 G. of the salt dissolved in 100 g. of water at 20°. The aqueous solution was neutral to litmus and yielded a pink precipitate with ammonium chloroplatinite.

Bromotriamminoplatinous picrate was obtained as irregular, microscopic, yellow plates when a solution of the bromide was treated with one mol. of ammonium picrate {Found: Pt, 35·2; N, 14·9; Br, 14·2. $[Pt(NH_3)_3Br](C_6H_2O_7N_3)$ requires Pt, 35·2; N, 15·2; Br, 14·4%}.

Nitrotriamminoplatinous Nitrate.—The very unstable nitrite of this series has been described by Tschugaev (*J.*, 1916, **109**, 1286). The much more stable *nitrate* has now been prepared. 2 G. of chlorotriamminoplatinous chloride were converted as above into a solution of chlorotriamminoplatinous nitrate. This was shaken for an hour with 0·970 g. (1 mol.) of silver nitrite and left overnight. The neutral, colourless filtrate was evaporated to small bulk in a vacuum over sulphuric acid and treated with excess of alcohol and ether, whereupon a voluminous white product separated (1·3 g. of acicular aggregates, very soluble in water) (Found: Pt, 55·3; N, 20·0; NO_3, 17·2. $[Pt(NH_3)_3(NO_2)]NO_3$ requires Pt, 55·1; N, 19·8; NO_3, 17·5%). (Sunlight should be excluded during precipitation, or some decomposition occurs.) The salt gave a salmon-pink chloroplatinite (microscopic, acicular aggregates).

Nitrotriamminoplatinous picrate was precipitated as slender yellow needles when a solution of the nitrate was treated with one mol. of ammonium picrate {Found: Pt, 37·2; N, 18·6. $[Pt(NH_3)_3(NO_2)](C_6H_2O_7N_3)$ requires Pt, 37·5; N, 18·9%}.

Nitratotriamminoplatinous Nitrate.—Cleve (*loc. cit.*, p. 64) claimed to have obtained this compound, in monohydrated form, by double decomposition between Cleve's salt and silver nitrate. Several preparations were made, refluxing with four mols. of silver nitrate, but in no case was the filtrate chlorine-free. The hemihydrated salt was readily obtained pure when chlorotriamminoplatinous chloride (2 g.) was shaken for an hour with 2·142 g. (2 mols.) of silver nitrate and 30 ml. of water. After being left overnight, the product was filtered and the filtrate, which was colourless and acid to litmus, was (*a*) treated with 400 ml. of alcohol and ether, whereby 1·9 g. of a white micro-crystalline precipitate were obtained (Found: Pt, 51·5; N, 18·8. $[Pt(NH_3)_3(NO_3)]NO_3,\frac{1}{2}H_2O$ requires Pt, 51·5; N, 18·5%), or (*b*) taken to dryness in a vacuum over sulphuric acid, the anhydrous salt then being obtained (Found: Pt, 52·7. Calc.: Pt, 52·7%).

Aquotriamminoplatinous chloroplatinite was obtained as an immediate acicular green precipitate when the aqueous solution of nitratotriamminoplatinous nitrate (*i.e.*, aquotriamminoplatinous nitrate) was treated with ammonium chloroplatinite (Found: Pt, 64·9; N, 7·3. Calc. for $[Pt(NH_3)_3(H_2O)]PtCl_4$: Pt, 64·9; N, 7·0%). No loss of weight or change of colour occurred when the compound was left over phosphoric oxide for two weeks. This compound and the corresponding bromoplatinite were described by Tschugaeff and Tschernjaeff (*Compt. rend.*, 1915, **161**, 792), and appear to be the only aquotriammines which exist in the solid state.

Picratotriamminoplatinous Picrate.—0·4 G. of chlorotriamminoplatinous chloride was treated as above with 2 mols. of silver nitrate and the resulting solution of aquotriamminoplatinous nitrate was added to 0·636 g. (2·2 mols.) of picric acid which had been converted into the ammonium salt. 0·75 G. of large needles was precipitated {Found: Pt, 28·1; N, 17·6 $[Pt(NH_3)_3(C_6H_2O_7N_3)](C_6H_2O_7N_3)$ requires Pt, 27·8; N, 18·0%}. There was no loss of weight at 100°.

Sulphatotriamminoplatinum could not be obtained by Cleve's method (*loc. cit.*) or by interaction of chlorotriamminoplatinous chloride or bromotriamminoplatinous bromide and silver sulphate. 2 G. of chlorotriamminoplatinous chloride were converted as above into an aqueous solution of aquotriamminoplatinous nitrate, which was concentrated to 25 ml. in a vacuum over sulphuric acid, treated with an equal volume of dilute sulphuric acid, and precipitated with alcohol and ether (120 ml.). The voluminous white microcrystalline product (1·6 g.) was dissolved in the minimum amount of water, and reprecipitated with alcohol and ether. The compound was fairly soluble, giving a slightly acid solution, but considerable heating and shaking were required to dissolve it. The solution yielded a green chloroplatinite. If dried overnight over soda–lime, the *compound* was monohydrated (Found: Pt, 54·6; N, 11·7; SO_4, 26·6. $[Pt(NH_3)_3(SO_4)],H_2O$ requires Pt, 54·2; N, 11·7; SO_4, 26·7%), but if it was left for a week in a vacuum over phosphoric oxide, a *hemihydrate* was obtained (Found: Pt, 55·6; N, 11·9; SO_4, 27·2. $[Pt(NH_3)_3(SO_4)],\frac{1}{2}H_2O$ requires Pt, 55·6; N, 12·0; SO_4, 27·3%).

Carbonatotriamminoplatinum.—3 G. of bromotriamminoplatinous bromide were shaken for 3 hours with silver carbonate freshly precipitated from 12 g. of silver nitrate and suspended in 50 ml. of water. After removal of silver bromide, the filtrate was ice-cooled and precipitated with alcohol and ether. 1·7 G. of very soluble white needles were obtained and dried over magnesium perchlorate (Found: Pt, 61·8; N, 13·6; C, 4·0; H, 3·1. $[Pt(NH_3)_3(CO_3)],\frac{1}{2}H_2O$ requires Pt, 61·9; N, 13·3; C, 3·8; H, 3·2%). The substance yielded a green chloroplatinite.

Oxalatotriamminoplatinum was obtained when 4 g. of silver nitrate were converted into silver oxalate and the moist product was shaken for 3 hours with 1 g. of bromotriamminoplatinous bromide and 15 ml. of water. The filtrate was free from bromine and was treated with alcohol and ether (100 ml.), yielding 0·55 g. of white needles, easily soluble to a neutral solution. The product was dried over soda–lime (Found: Pt, 55·3; N, 11·7; C_2O_4, 24·7; H_2O, 4·7. $[Pt(NH_3)_3(C_2O_4)],H_2O$ requires Pt, 55·4; N, 11·9; C_2O_4, 25·0; H_2O, 5·1%). The compound was completely dehydrated over phosphoric oxide. A pure product could not be obtained by treating hydroxotriamminoplatinous hydroxide with one mol. of oxalic acid, owing to contamination with an acid oxalate. The oxalato-triammine yielded a green chloroplatinite.

Hydroxotriamminoplatinous hydroxide was obtained in aqueous solution when 1 g. of bromotriamminoplatinous bromide was left in contact with freshly prepared moist silver oxide (from 4 g. of silver nitrate) for 5 hours, with occasional trituration. The colourless, strongly alkaline filtrate was found to be free from bromine and gave the theoretical yield of picratotriamminoplatinous picrate when treated with 2 mols. of picric acid. The hydroxide could not be obtained in the solid state, decomposition occurring when the solution was taken to dryness over sulphuric acid or precipitated with alcohol and ether. If chlorotriamminoplatinous chloride was substituted for the bromo-bromide, the product was not chlorine-free, even after boiling with silver oxide. The hydroxide might have been expected to yield, with 1 equiv. of acid, hydroxotriamminoplatinous salts, analogous to the acidohydroxodiammines described in Part IX. These could not, however, be isolated, probably owing to their great solubility.

Ethylenediaminotriamminoplatinous chloride was obtained by triturating 1 g. of chlorotriamminoplatinous chloride with a little ethylenediamine hydrate for a few minutes till a white paste was obtained. Alcohol was then added, and the product transferred to a filter and washed with alcohol to remove excess of ethylenediamine hydrate. It was dried in a vacuum over soda–lime (Found: Pt, 51·6; N, 18·8; Cl, 18·4. $[Pt(NH_3)_3en]Cl_2$ requires Pt, 51·7; N, 18·6; Cl, 18·8%). The solid product had no smell; it lost 4·8% of its weight when heated at 100° (Calc. for loss of $1NH_3$: 4·5%). The aqueous solution was only faintly alkaline to litmus, but could be titrated with standard acid, the end-point corresponding to neutralisation of exactly 4·5% of ammonia. The same amount of ammonia was removed by boiling the aqueous solution for 15 mins.

Action of Ammonium Picrate on Ethylenediaminotriamminoplatinous Chloride.—3·3 Mols. of ammonium picrate were used, giving an immediate precipitate of large yellow needles in 75% yield {Found: Pt, 19·9; N, 19·8. $[Pt(NH_3)_3enH(C_6H_2O_7N_3)](C_6H_2O_7N_3)_2$ requires Pt, 19·7; N, 19·8%}.

Ethylenediaminodiamminoplatinous picrate was obtained when 3 mols. of ammonium picrate were added to a solution of ethylenediaminotriamminoplatinous chloride which had been boiled for 20 minutes to expel one mol. of ammonia {Found: Pt, 26·0; N, 18·7. $[Pt(NH_3)_2(H_2N{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2)](C_6H_2O_7N_3)_2$ requires Pt, 26·2; N, 18·8%}.

p-*Values.*—The colorimetric method was used, with bromophenol-blue as indicator. For M/256-solutions, the values obtained were: $[Pt(NH_3)_3(NO_3)]NO_3$, pH 4·2; $[Pt(NH_3)_3(SO_4)]$, pH 4·4.

Electrical Conductivities at 25°.—In the tables, v is the reciprocal of the concentration in g.-mols. per litre and λ is the corrected molecular conductivity in mhos. Measurements in Table I were made (*a*) immediately after solution, (*b*) after 24 hours. The conductivities of the chlorotriamminoplatinous salts increased with time and had reached equilibrium after 24 hours. The (*a*) values for these salts have been obtained by extrapolation to zero time. The λ–$c^{1/3}$ graphs drawn from these (*a*) values indicate negligible aquation for dilutions up to 256 litres, increasing rapidly, however, on further dilution (see Part II, *J.*, 1925, **127**, 2105). At a dilution of 1024 litres, the (*a*) value for the chloride indicates 5% aquation, increasing to 15% at equilibrium. For bromotriamminoplatinous bromide, the values obtained immediately after solution gave a linear graph, indicating absence of aquation. At a dilution of 1024 litres, the equilibrium value indicated only 3% aquation.

TABLE I.

Acido-triammines which dissolved without aquation.

v	32.	64.	128.	256.	512.	1024.	∞
λ for $[Pt(NH_3)_3Cl]Cl$ (*a*)	100·4	102·6	104·4	106·0	108·8	116·2	—
$[Pt(NH_3)_3Cl]Cl$ (*b*)	100·4	103·7	106·5	109·4	117·5	130·5	—
,, $[Pt(NH_3)_3Cl]NO_3$ (*a*)	107·1	109·5	111·4	113·0	115·2	117·8	—
$[Pt(NH_3)_3Cl]NO_3$ (*b*)	107·1	117·8	122·8	134·3	146·6	160·2	—
,, $[Pt(NH_3)_3Br]Br$ (*a*)	—	—	109·4	113·0	116·1	118·2	—
$[Pt(NH_3)_3Br]Br$ (*b*)	—	—	111·5	116·0	120·0	122·8	—
,, $[Pt(NH_3)_3(NO_2)]NO_3$	101·7	107·3	111·6	115·0	117·9	120·1	125·8 (n = 1·48)

The values for nitrotriamminoplatinous nitrate showed no increase on standing, and the linear λ–$c^{1/3}$ graph showed that no aquation occurred on dilution. This might be expected, since aquation would necessarily be preceded by conversion of the nitro- into the nitrito-triammine; λ_∞ for this compound was obtained by means of the $1/\lambda$–$(c\lambda)^{n-1}$ graph, and gives a value of 54·4 mhos for the mobility of the nitrotriamminoplatinous ion at 25°, 71·4 mhos being taken as the mobility of the nitrate ion. The values for nitratotriamminoplatinous nitrate showed no increase on standing and indicate immediate and complete aquation to $[Pt(NH_3)_3(H_2O)](NO_3)_2$. They differ but little from the values previously recorded for the *cis*-dinitratodiammine, which has been shown to dissolve as *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$ (see Part IX, *loc. cit.*). The values recorded for picratotriamminoplatinous picrate agree well with the previously recorded value of 182·6 mhos for the *cis*-dipicratodiammine at a dilution of 1024 litres, and indicate complete aquation to aquotriamminoplatinous picrate. The data obtained for the sulphatotriammine increased on standing, reaching equilibrium in an hour. In this case, aquation was evidently slower, but conversion into $[Pt(NH_3)_3(H_2O)]SO_4$ was fairly complete. The values agree closely with those previously recorded for the *cis*-sulphatodiammine, which has similarly been shown to dissolve as

TABLE II.

Acido-triammines which dissolved with complete or substantial aquation.

v	64.	128.	256.	512.	1024.
λ for $[Pt(NH_3)_3(NO_3)]NO_3$	—	232·1	250·5	259·0	267·0
,, $[Pt(NH_3)_3(C_6H_2O_7N_3)](C_6H_2O_7N_3)$	—	—	—	178·3	190·4
,, $[Pt(NH_3)_3(SO_4)]$ equilibrium values	—	—	165·4	205·9	229·6
,, $[Pt(NH_3)_3(CO_3)]$,,	69·1	79·4	86·4	91·3	104·4
,, $[Pt(NH_3)_3(C_2O_4)]$,,	42·3	44·6	46·6	48·1	48·9

cis-$[Pt(NH_3)_2(H_2O)_2]SO_4$. The conductivities of the carbonatotriammine increased on standing, reaching equilibrium in from 15 to 45 minutes, according to the concentration. At a dilution of 256 litres, this increase amounted to 15% in 25 minutes. Even at the lower concentrations, the equilibrium values indicate less than 50% aquation. In the case of the oxalato-triammine, the increase in conductivity on standing was much less (2% at a dilution of 256 litres) and equilibrium was reached in 20 minutes. Aquation was, however, very incomplete, amounting only to about 20% even at the lower concentrations.

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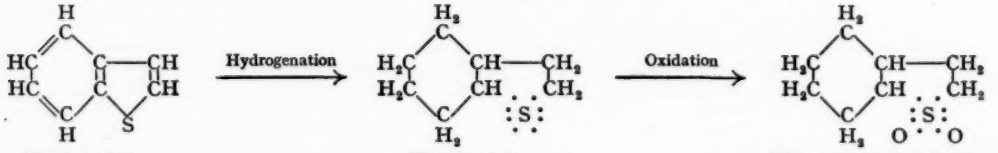
387. *Studies in the Detoxication of Catalyst Poisons. Part VIII. Thionaphthen and the Thiophthens.*

By E. B. MAXTED and A. G. WALKER.

The suppression of the toxicity of thionaphthen towards metallic hydrogenation catalysts, by converting the poison into a shielded and therefore non-toxic form, has been carried out by a procedure similar to that previously used for thiophen (Part V). This conversion is of interest in connection with the catalytic hydrogenation of technical naphthalene. The detoxication of two of the isomers of thiophthen has also been studied.

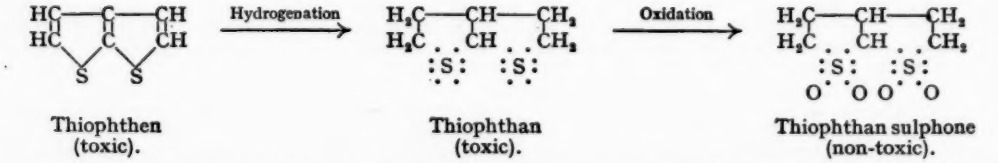
THE detoxication of the catalyst poisons which occur in naphthalene is of considerable importance on account of the extent to which naphthalene is hydrogenated industrially. Coal-tar naphthalene ordinarily contains from 0·2 to 0·4% of total sulphur. Thionaphthen (I) is certainly present as a major constituent and has been isolated from naphthalene by Weissberger and Kruber (*Ber.*, 1920, **53**, 1551); and it may be noted that the relatively late actual isolation of this poison—the presence of which had long been expected from an analogy to the occurrence of thiophen in benzene—was mainly due to unusual separation difficulties and followed varying reports by earlier workers (see, *e.g.*, Boes, *Apothek. Ztg.*, 1902, **17**, 565) on the occurrence of thionaphthen in tars of various origins. In addition to thionaphthen, it is probable that thiophthens, (II) and its isomers, also occur to some extent in the sulphur poisons of naphthalene, since these condensed thiophens are known to be formed by pyrogenetic reactions similar to those which are capable of giving thionaphthen.

(I.) (II.)



Thionaphthen (toxic). Thionaphthan (toxic). Thionaphthan sulphone (shielded non-toxic structure).

and



Thiophthen (toxic). Thiophthan (toxic). Thiophthan sulphone (non-toxic).

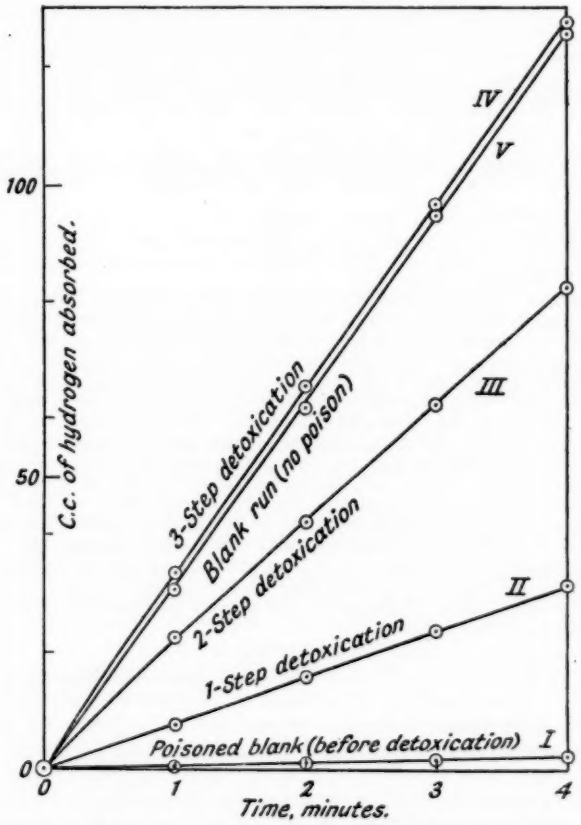
The present work, which relates to the detoxication of thionaphthen and the thiophthens added in known amounts to an artificial hydrogenation system, has been carried out in order to

obtain preliminary information which can be utilised in a more detailed study of the detoxication of technical naphthalene. It has been found that all these poisons can be detoxicated by the treatment previously used for thiophen (*J.*, 1947, 624), namely, by a short preliminary hydrogenation followed by the addition of an oxidising detoxicant. As was found for thiophen, this preliminary hydrogenation stage—during which the cyclic sulphur compound, by virtue of its preferential adsorption as a poison on the catalyst, undergoes preferential hydrogenation to a product which lends itself more easily to subsequent oxidation than the original poison—is a necessary part of the detoxication procedure; and the suppression of the toxic character of the poison does not take place if the hydrogenation stage is omitted, since these cyclic thiophen derivatives, like thiophen itself, do not readily form sulphones directly. From an analogy with the corresponding case of thiophen, the course of the detoxication is probably as shown below, the electronic state of the sulphur atoms in the intermediate and in the final stages of the detoxication being indicated in the usual way.

Experimental.

Detoxication of Thionaphthen.—The detoxication procedure closely resembled that already described for thiophen (*q.v.*). Crotonic acid was, as before, used as a convenient unsaturated substance for

Detoxication of thionaphthen.



following the suppression of the toxicity of the thionaphthen as a result of the detoxication treatment; and the standard hydrogenation system taken for each run consisted of 10 c.c. of a N-solution of crotonic acid in acetic acid, 5×10^{-6} g.-mol. of thionaphthen, 0·075 g. of stock platinum catalyst, and 2 c.c. of water, including water added with the detoxicant. The above amount of thionaphthen, in its original toxic state, was sufficient to reduce the hydrogenation velocity down to a small fraction (*ca.* 2%) of the rate in the absence of the poison. The main hydrogenation runs were carried out in a shaker, under standardised conditions, at 27° and at atmospheric pressure.

The series of runs summarised in the figure show the results obtained by using small quantities of a detoxicating reagent containing permolybdic acid, the reagent being made up, as previously described, by acting on molybdic acid with hydrogen peroxide. The poisoned charge in the hydrogenation pipette was first subjected to the usual short (2 mins.) preliminary hydrogenation, following which 0·5 c.c. of

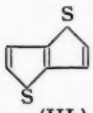
the detoxicating reagent, containing 3×10^{-5} g.-mol. of permolybdic acid, was added, any excess of per-acid or hydrogen peroxide being then destroyed by heating to 80° before the main hydrogenation run by means of which the extent of the detoxication was measured. In order to reach a state corresponding with a complete suppression of the toxicity of the thionaphthen it was in general necessary to repeat the above two-stage detoxication treatment several times before carrying out the main hydrogenation run. Curve I shows the hydrogenation velocity of the standard poisoned charge before detoxication. Curves II, III, and IV give the hydrogenation rates after a detoxication treatment consisting respectively of one, two, and three short hydrogenations followed, after the first hydrogenation, by the addition of 3×10^{-5} g.-mol. of permolybdic acid and, after each of any subsequent hydrogenations, by 0·075 g. (*ca.* 2×10^{-3} g.-mol.) of hydrogen peroxide. The number of detoxication treatments applied before the carrying out of the main hydrogenation run is, in conformity with previous papers, referred to in the figure as one-, two-, and three-step treatment, respectively. Curve V shows the hydrogenation velocity given by a blank charge from which the thionaphthen had been omitted. It will be seen that complete detoxication was reached after a 3-step treatment: indeed, the hydrogenation rate had then risen to a value slightly greater than that of the blank run. This effect has frequently been observed in the present type of work and is probably due to the cleaning up also of small traces of original poison contained in the platinum black.

Hydrogen peroxide, which was also tried for the oxidation phase, was found not to be a very effective detoxicant in the absence of molybdenum compounds (see also Parts II and III); but if, in a treatment involving more than one application of the hydrogenation–oxidation process, molybdenum is already present in the system from the first step, it is sufficient in the oxidation phase of any subsequent steps to add hydrogen peroxide alone, since permolybdic acid is regenerated. The oxidation phase of all steps, including the first, can on the other hand be effectively carried out by small quantities of dilute nitric acid (cf. Part II for the use of this reagent in the detoxication of cystein, which, however, requires no preliminary hydrogenation). Table I shows the effect of a 2-step and a 3-step detoxication of standard hydrogenation charges—containing the usual amount of thionaphthen—with N-aqueous nitric acid (5×10^{-4} g.-mol. at each step). By 100% detoxication is understood the complete re-attainment by the poisoned system of a hydrogenation rate equal to that given in an unpoisoned blank run.

TABLE I.

Number of detoxication steps.	Hydrogenation rate, in c.c. per min., after detoxication.	Detoxication obtained, %.
No detoxication	0·7	—
2	26·6	83
3	32·7	102
(Blank run omitting poison	32·0	100)

As will be seen from the table, complete detoxication was given by a 3-step treatment. The use of dilute nitric acid as a detoxicant has, however, the disadvantage that the excess of the reagent cannot be destroyed by heating and thus remains in the system; although it was shown in the previous work on cystein that the two possible complications introduced by using nitric acid—*i.e.*, the possible destruction of some of the unsaturated substance by oxidation at its double bond or, secondly, the taking up of hydrogen at an appreciable rate by the residual traces of dilute nitric acid during the hydrogenation runs—apparently do not occur to a measurable extent under the conditions employed.



(III.)

Detoxication of the Thiophthens.—Of the three known isomers, specimens of two only, namely those of the structures (II) and (III) were available and were supplied by the courtesy of Dr. E. C. Holdsworth. These will be referred to as thiophthen I and II respectively.

The detoxication of these poisons was carried out in the same way as for thionaphthen. The poisoned charge contained in each case 5×10^{-6} g.-mol. of thiophthen, this being sufficient to poison the hydrogenation rate down to about 0·8 c.c. per minute, the unpoisoned rate under the conditions of this series of runs being 41·3 c.c. per minute. The progress of the detoxication, measured by the movement of this very low rate towards the unpoisoned velocity given in a blank run with the omission of the poison, is summarised in Table II, the amounts of permolybdic or nitric acid used for the oxidation steps being as already given.

TABLE II.

Poison.	Detoxicant.	Number of steps.	Hydrogenation rate, c.c. of H_2 per min.	Detoxication, %.
Thiophthen I	Permolybdic acid	None	0·82	—
		1	12·8	31·0
		2	32·4	78·4
		3	40·6	98·3
		4	41·5	100·5
(Blank run without addition of thiophthen			41·3	100)
Thiophthen II	Permolybdic acid	None	0·85	—
		1	4·2	10·2
		2	25·4	61·5
		3	34·7	84·0
		4	35·6	86·2
Thiophthen I	Nitric acid	1	17·1	41·4
		2	35·1	85·0
		3	38·1	92·2
Thiophthen II	Nitric acid	1	10·9	26·4
		2	33·1	80·1
		3	37·4	90·6

It will be seen that complete detoxication of thiophthen I was obtained by a 4-step treatment with permolybdic acid. Thiophthen II is apparently more resistant, only 86% detoxication being reached by a similar treatment. The use of dilute nitric acid for the oxidation stage in the detoxication of both of these poisons was, on the whole, less successful than that of permolybdic acid.

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UNIVERSITY OF BRISTOL. [*Received, January 3rd,* 1948.]

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388. *The Addition of Hydrogen Sulphide to 2-Phenyl-Δ²-oxazoline and Benzoylethyleneimine: Attempted Synthesis of Fused Thiazolidine–Butyroazlactone Ring Systems.*

By ALAN A. GOLDBERG and WILLIAM KELLY.

2-Phenyl-Δ²-oxazoline reacts additively with hydrogen sulphide to yield N-(2-*hydroxyethyl*)*thiobenzamide*.

Addition of hydrogen sulphide to the isomeric benzoylethyleneimine yields 2-*benzamidoethylthiol*.

General observations of a quantitative nature have been made upon the thermal isomerisation of benzoylethyleneimine to 2-phenyl-Δ²-oxazoline and upon the stabilities of the oxazoline and ethyleneimine heterocycles towards additive reagents.

Use has been made of these observations to attempt the synthesis of compounds containing the fused thiazolidine–butyroazlactone ring system. Benzeneazoacetoacetyl chloride was converted into the corresponding ethyleneimide and the latter brought into reaction with hydrogen sulphide. Fission of the heterocycle with addition of hydrogen sulphide took place, followed by simultaneous cyclisation to a ketotetrahydro-1 : 4-thiazine.

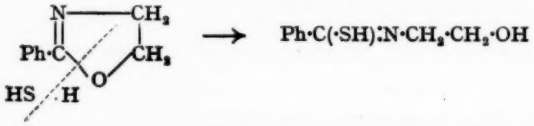
2-ACYLAMIDOETHYLTHIOLS were required for the synthesis of compounds containing the fused thiazolidine–butyroazlactone ring system for examination as bacterial inhibitors. 2-Benzamidoethylthiol, which was considered to be the most accessible of these compounds for model experiments, is unobtainable either by the action of alkali hydrogen sulphides on benz-2-bromoethylamide or by the benzoylation of 2-aminoethylthiol; accordingly, attention was turned to possible routes *via* the addition of hydrogen sulphide to benzoylethyleneimine and to 2-phenyl-Δ²-oxazoline. It is known that ethyleneimine reacts with water to yield ethanolamine (Gabriel and Stelzner, *Ber.*, 1895, **28**, 2929), with hydrogen sulphide to give 2-aminoethylthiol (Mills and Bogert, *J. Amer. Chem. Soc.*, 1940, **62**, 1177), and with sulphurous acid to yield taurine (Gabriel, *Ber.*, 1888, **21**, 2665); alternatively, 2-phenyloxazoline hydrochloride reacts with water to yield 2-aminoethyl benzoate and with concentrated hydrochloric acid to give benz-2-chloroethylamide (Gabriel and Heymann, *Ber.*, 1890, **23**, 2495). All these reactions constitute a scission of the heterocycle and addition of the other reactant.

It was found that hydrogen sulphide reacts additively with 2-phenyl-Δ²-oxazoline to yield a compound $C_9H_{11}ONS$, m. p. 96°, which gave no coloration with sodium nitroprusside and so did not appear to contain a thiol grouping. Treatment of the compound with sodium ethoxide and ethyl iodide effected immediate evolution of ethylthiol and formation of 2-phenyloxazoline; similarly, treatment with sodium ethoxide and benzyl chloride yielded benzylthiol and 2-phenyloxazoline. The elimination of thiol during the alkylation suggested the intermediate formation of an iminothioether, and the production of phenyloxazoline showed the presence of the Ph·C·N·CH_2·CH_2·O· complex in the original compound which was accordingly formulated as N-(2-*hydroxyethyl*)*thiobenzamide*. The proof of this structure was furnished by rational synthesis by a method developed from the work of Delépine (*Compt. rend.*, 1911, **153**, 281); ethyl thionbenzoate and ethanolamine condensed to yield a compound, m. p. 96°, identical with that obtained by the addition of hydrogen sulphide to phenyloxazoline.

2-Phenyloxazoline is an *ON*-ethylene-substituted benziminoether and accordingly would be expected to exhibit the general properties of an iminoether. Although the compound is remarkably stable towards cold water, it reacts at high temperatures to give benz-2-hydroxyethylamide; the addition could take place by rupture of, and addition of water to, either the 1 : 2- or the 1 : 5-oxygen–carbon bond of the heterocycle. 2-Phenyloxazoline monohydrochloride reacts with boiling water to yield 2-aminoethyl benzoate hydrochloride (Gabriel and Heymann, *loc. cit.*), a reaction which must take place by rupture of, and addition of water to, the 2 : 3-carbon–nitrogen double bond. These reactions resemble the well-known hydrolytic fission of iminoethers to amide and ester, respectively. Anhydrous phenyloxazoline

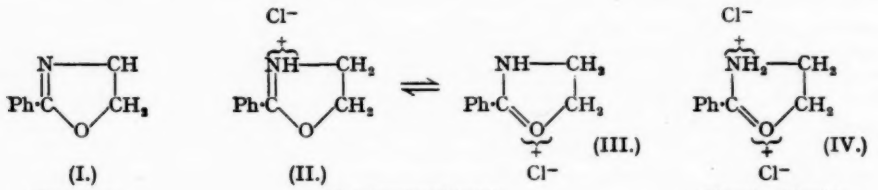
hydrochloride when heated to its melting point is rearranged quantitatively into benz-2-chloroethylamide (Wislicenus and Körber, *Ber.*, 1902, **35**, 164), a transformation completely comparable to the thermal degradation of an iminoether hydrochloride R·C(:NH)·OR$_1$,HCl into the amide R·CO·NH$_2$ and alkyl halide R$_1$Cl (Pinner, " Die Imidoether ", 1892, p. 5); this degradation must take place by rupture of the 1 : 5-oxygen–carbon bond. It has been found during the present work that concentrated anhydrous hydrogen chloride reacts with phenyloxazoline at 0° with almost quantitative formation of benz-2-chloroethylamide. Since these are conditions under which intramolecular rearrangements similar to those observed by Chapman (*J.*, 1925, **127**, 1992) would not take place, it must be deduced that the transformation is effected by rupture of, and addition of hydrogen chloride to, the 1 : 5-oxygen–carbon bond of the oxazoline.

It is evident that scission of the Δ^2-oxazoline heterocycle and addition of hydrogen sulphide can take place only by opening of the 1 : 2-oxygen–carbon bond, thus :

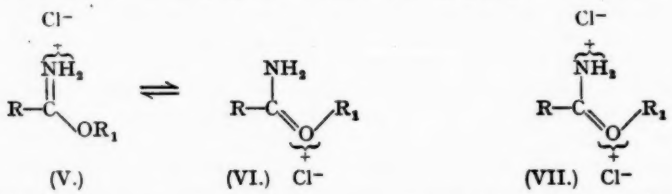


and by comparison it would seem reasonable to assume that formation of benz-2-hydroxyethylamide by addition of water to phenyloxazoline base takes place by rupture of the 1 : 2- and *not* the 1 : 5-oxygen–carbon bond. It is noteworthy that the 2 : 3-carbon–nitrogen bond of the oxazoline heterocycle is stable towards hydrogen sulphide, whereas benziminoether base readily condenses with hydrogen sulphide with elimination of ammonia to give high yields of ethyl thionbenzoate (Matsui, *Mem. Coll. Eng. Kyoto*, 1903—1908, **1**, 285; *Centr.*, 1909, II, 423; Delépine, *Bull. Soc. chim.*, 1911, **9**, 904).

The foregoing reactions of 2-phenyloxazoline may be rationalised by formulation of the monohydrochloride as a resonance hybrid of the ammonium and the oxonium form, (II) and (III), respectively. The existence of an ammonium–oxonium dihydrochloride (IV) may also be



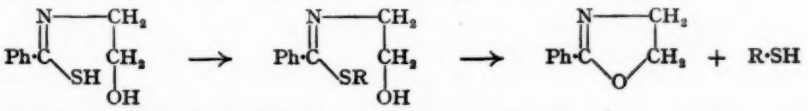
postulated but is not necessary. The position of opening of the oxazoline heterocycle would be expected to be governed by the internal conditions, *e.g.*, stereochemical or electromeric strain, and external influences such as proton availability or presence of solvent, which might stabilise either the ammonium or the oxonium phase of the monohydrochloride or promote formation of the ammonoum–oxonium dihydrochloride. It is easy to conceive that the ammonium form (II) would on hydrolysis yield 2-aminoethyl benzoate hydrochloride, that the oxonium form (III) on thermal decomposition would yield benz-2-chloroethylamide, and that the ammonium–oxonium dihydrochloride in the presence of concentrated hydrogen chloride would yield benz-2-chloroethylamide. It is of passing interest that iminoether hydrochlorides may in general be formulated upon the same lines, *i.e.*, as resonance hybrids of the ammonium and oxonium forms (V and VI), which would account for the hydrolytic degradation under different external conditions to ester R·CO$_2$R$_1$ or amide R·CO·NH$_2$ by rupture of the double bond attached



to the polarised focus of the ammonium or the oxonium phase, respectively. The influence of excess of hydrochloric acid, *i.e.*, effect of pH value, on the almost quantitative hydrolysis

of benziminoether hydrochloride into ethyl benzoate was observed by Schlesinger (*Amer. Chem. J.*, 1908, **39**, 719) and McCracken (*ibid.*, p. 586; compare also McKee, *ibid.*, 1901, **26**, 262) but, although formation of amide during the hydrolysis of iminoethers is well known, the literature does not appear to state the precise conditions which favour production of amide. It has now been shown that while benziminoether base on prolonged heating with water or aqueous alcohol at the pH value (8·0) created by the base itself gives a *ca.* 50% yield of benzamide, yet in the presence of sufficient benzyltrimethylammonium hydroxide to maintain a pH value of 11·0 the amount of benzamide is increased to *ca.* 60% of theory; apparently very little ethyl benzoate and a considerable amount of phenyl cyanide is formed at this pH value. In addition, if iminoether hydrochlorides in the solid phase are considered to exist in the oxonium form, the thermal degradation to amide $R{\cdot}CO{\cdot}NH_2$ and alkyl halide R_1Cl is more readily understandable. The unstable iminoether hydrochloride–hydrogen chloride complexes mentioned by Pinner (*op. cit.*, pp. 53, 55, 65) and assumed by him to be 1-chloro-1-aminoether hydrochlorides, $R{\cdot}CCl(NH_2){\cdot}OR_1,HCl$, are most probably dihydrochlorides of the ammonium–oxonium type (VII).

Alkylation of *N*-(2-hydroxyethyl)thiobenzamide apparently takes place thus:



the intermediate *N*-(2-hydroxyethyl)-*S*-alkylthiobenziminoether immediately undergoing cyclisation to phenyloxazoline with elimination of alkylthiol. That production of phenyloxazoline is a *direct* intramolecular cyclisation not involving the solvent (alcohol) is shown by the fact that benzylation of N-iso*propylthiobenzamide* in the presence of sodium ethoxide and alcohol gives a high yield of S-*benzyl*-N-iso*propylthiobenziminoether*, which is a remarkably stable compound (contrast the instability of unsubstituted iminothioether bases; Autenrieth and Brüning, *Ber.*, 1903, **36**, 3465; Bernthsen, *Annalen*, 1879, **197**, 350).

Gabriel and Stelzner (*loc. cit.*) obtained benzoylethyleneimine, m. p. 1°, by benzoylation of ethyleneimine and showed that the compound rearranged to phenyloxazoline on distillation at 240°/760 mm. It has now been found that benzoylation of ethyleneimine at 0° and isolation at a low temperature yields a product of m. p. 5°, this being raised to 8—9° by partial freezing and draining away of liquid. It is believed that this material represents pure benzoylethyleneimine substantially free from phenyloxazoline.

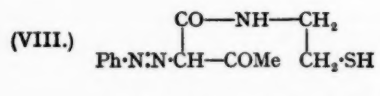
Action of Cold Dilute Hydrochloric Acid on Phenyloxazoline and Benzoylethyleneimine.—Phenyloxazoline is stable towards cold dilute hydrochloric acid; the base readily dissolves in the reagent and after standing at room temperature for 4 hours may be recovered by basification and ether extraction in 85% yield. On the other hand, on shaking the insoluble benzoylethyleneimine with cold dilute hydrochloric acid an immediate exothermic reaction develops with separation of benz-2-chloroethylamide. Since both the " crude " (m. p. 5°) and the " purified " (m. p. 8°) material give a *ca.* 75% yield of benzchloroethylamide it is believed that these represent benzoylethyleneimine, free from 2-phenyloxazoline, and that during the reaction *ca.* 25% of the former is converted by addition of water into the soluble benzhydroxyethylamide or by isomerisation into the oxazoline.

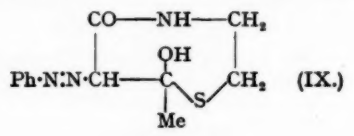
Although at 55° benzoylethyleneimine is stable for several hours, yet at 115° isomerisation into phenyloxazoline is considerable in 2 hours; at the b. p. 125°/12 mm. conversion into phenyloxazoline is very rapid, with distillation of liquid consisting of *ca.* 70% of phenyloxazoline and 30% of benzoylethyleneimine.

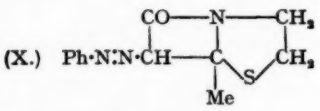
Addition of Hydrogen Sulphide to Benzoylethyleneimine.—In contrast with phenyloxazoline, benzoylethyleneimine reacts *rapidly* with hydrogen sulphide to yield 2-*benzamidoethylthiol*; this compound gives an intense coloration with sodium nitroprusside and on benzylation yields benzyl 2-benzamidoethyl sulphide. The latter was identified by hydrolysis to benzyl 2-aminoethyl sulphide, which on phthaloylation yielded benzyl 2-phthalimidoethyl sulphide identical with that obtained by the benzylation of 2-phthalimidoethylthiol (Michels, *Ber.*, 1892, **25**, 3050). It is noteworthy that benzyl 2-aminoethyl sulphide is most conveniently obtained by direct benzylation of 2-aminoethylthiol, thus eliminating the difficult hydrolysis of the phthalimido-derivative described by Michels.

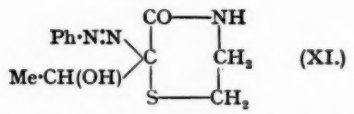
In order to utilise the foregoing reactions to obtain compounds potentially convertible into substances containing the fused thiazolidine–butyroazlactone ring system, it was necessary to prepare an acylamidoethylthiol containing a keto-group in the acyl residue; the benzeneazo-

acetoacetyl grouping was selected as the most easily accessible acylating radical. Benzeneazoacetoacetic acid was converted into the acid chloride and this reacted with ethyleneimine under conditions known to yield the acylethyleneimide and not the oxazoline. It was thought that addition of hydrogen sulphide to the product would yield 2-(benzeneazoacetoacetamido)ethylthiol (VIII) which would undergo internal thiol–ketone condensation to give the seven-membered ring compound (IX) which might be dehydrated to yield the thiazolidine (X).









Benzeneazoacetoacetic acid was converted *via* its *acid chloride* into *benzeneazoacetoacetylethyleneimide*. The latter reacted exothermically with hydrogen sulphide—a reaction indicating an ethyleneimide and not an oxazoline—to yield a *compound* $C_{12}H_{15}O_2N_3S$. This was stable to alcoholic hydrogen chloride and to aqueous sodium hydroxide and gave no coloration with sodium nitroprusside. All attempts to effect dehydration were unsuccessful. The compound would therefore appear to be, not the expected thiol (VIII), but a condensate derived from the latter by a cyclisation involving the terminal thiol radical and (*a*) the keto-group (compound IX) or (*b*) the double bond of the enol form of the ketone (compound XI). The stability of the substance would lend support to the 3-keto-2 : 3 : 5 : 6-tetrahydro-1 : 4-thiazine formulation (XI).

Experimental.

2-Phenyloxazoline (cf. Gabriel and Heyman, *loc. cit.*).—Benz-2-bromoethylamide (87 g.; Goldberg, *J.*, 1945, 828) was suspended in 5N-sodium hydroxide (80 c.c.) and alcohol (150 c.c.), and the mixture heated with shaking to 40—45° and kept at room temperature for ½ hour. Water (1 l.) was added, and the precipitated oil extracted with ether (250 c.c.); the ethereal extract, after drying ($MgSO_4$) and distillation, yielded 2-phenyloxazoline as a colourless oil (40 g.), b. p. 122—124°/14 mm., m. p. 12° (Found, in redistilled sample: C, 73·5; H, 6·3; N, 9·7. Calc. for C_9H_9ON: C, 73·4; H, 6·1; N, 9·5%). The picrate separated from alcohol in stout yellow prisms, m. p. 186° (Found: N, 15·1. Calc. for $C_{15}H_{12}O_8N_4$: N, 14·9%).

Phenyloxazoline (13 g.) was also obtained as a colourless oil by refluxing benz-2-bromoethylamide (22·6 g.) in anhydrous methanol (150 c.c.) for 3 hours with anhydrous potassium cyanide (13 g.) and a trace of copper powder; none of the expected β-benzamidopropionitrile was obtained.

2-Phenyloxazoline is readily soluble in cold dilute hydrochloric acid. On addition of 1 mol. of hydrochloric acid to 1 mol. of phenyloxazoline suspended in water, the aqueous phase buffers between pH 4·0 and pH 3·0; a 15% solution of phenyloxazoline hydrochloride in water has pH 2·4—2·6.

2-Phenyloxazoline methiodide was obtained by refluxing the base (2 g.) and methyl iodide (2 c.c.) for ½ hour; it separated from alcohol–ether in slender cream needles, m. p. 116—117° (Found: N, 4·9; I, 43·5. $C_{10}H_{12}ONI$ requires N, 4·8; I, 43·9%). The methiodide was recovered unchanged after refluxing for 20 hours with excess of methyl iodide.

Benzoylation of 2-Phenyloxazoline in Aqueous Medium: 2-Benzamidoethyl Benzoate.—Benzoyl chloride (0·9 g.) was added portionwise to a stirred mixture of water (15 c.c.), 2-phenyloxazoline (1·0 g.), and sodium hydrogen carbonate (1·0 g.) at 10—15°. After 3 hours' stirring the precipitate (1·3 g., m. p. 76—82°) was collected and recrystallised from aqueous methyl alcohol, 2-benzamidoethyl benzoate being obtained, m. p. 88—89° alone and in admixture with material obtained by the benzoylation of ethanolamine (Knorr, *Ber.*, 1897, **30**, 909) (Found: C, 71·7; H, 5·6; N, 5·3. Calc. for $C_{16}H_{15}O_3N$: C, 71·4; H, 5·6; N, 5·2%). The same compound was obtained by addition of benzoyl chloride to a solution of phenyloxazoline in anhydrous pyridine and then pouring the mixture into water.

Stability of 2-Phenyloxazoline towards Cold Dilute Hydrochloric Acid.—A solution of 2-phenyloxazoline (10 g.) in water (50 c.c.) and 4·32N-hydrochloric acid (31·2 c.c.; 2 mols.) was kept at 15° for *x* hours. The solution was basified with 5N-sodium hydroxide, extracted with ether, and the dried ethereal extract distilled. The amount of 2-phenyloxazoline recovered was as follows:

Time (*x* hours)	1	4	48	192
Amount recovered, g.	9·0	8·5	4·5	(gum)

In each case the recovered phenyloxazoline had b. p. 122—124°/12 mm. and the picrate had m. p. 184—186° alone and in admixture with authentic material.

2-Phenyloxazoline Hydrochloride.—Anhydrous alcoholic hydrogen chloride (10%; 5 c.c.) was added to a solution of phenyloxazoline (2·0 g.) in dry ether (30 c.c.). The precipitate was collected immediately, washed with dry ether, and dried in a vacuum at room temperature; the hydrochloride was obtained as a white crystalline powder, m. p. 80—81°. When dissolved in water and the latter distilled off at 15°

at reduced pressure the salt was recovered unchanged, m. p. 80° (Found : N, 7·7; Cl, 19·1. Calc. for C_9H_9ON,HCl : N, 7·6; Cl, 19·3%).

Decomposition of Phenyloxazoline Hydrochloride by Water : 2-Aminoethyl Benzoate.—A solution of phenyloxazoline (10·2 g.) in water (70 c.c.) containing 1 equiv. of hydrochloric acid was refluxed for 1 hour and then evaporated to dryness on the water-bath during 6 hours. The solid residue of 2-aminoethyl benzoate hydrochloride was collected, washed with acetone, and dried at 15°; yield 10·8 g., m. p. 129—130° (Found : N, 7·2; Cl, 17·8. Calc. for $C_9H_{12}O_2NCl$: N, 7·0; Cl, 17·6%). The m. p. in admixture with 2-phenyloxazoline hydrochloride was 62—67°. The picrate, obtained by mixing hot aqueous solutions of the foregoing hydrochloride and picric acid, separated from water in yellow acicular plates, m. p. 202—204° alone and at 168—172° in admixture with phenyloxazoline picrate (Found : C, 46·1; H, 3·8; N, 14·5. Calc. for $C_{15}H_{14}O_9N_4$: C, 45·7; H, 3·6; N, 14·2%).

Decomposition of Phenyloxazoline Base by Water : Benz-2-hydroxyethylamide.—2-Phenyloxazoline (6·4 g.) was refluxed with water (25 c.c.) for 20 hours, and the resulting solution evaporated almost to dryness on the water-bath. The residual solid after draining on porous pot yielded crude benz-2-hydroxyethylamide (6·0 g.), m. p. 52—56°, which crystallised from ethyl acetate in white needles, m. p. 66° alone and in admixture with material obtained by partial hydrolysis of 2-benzamidoethyl benzoate (Fränkel and Cornelius, *Ber.*, 1918, **51**, 1657) (Found : N, 8·8. Calc. for $C_9H_{11}O_2N$: N, 8·5%).

Addition of Anhydrous Hydrogen Chloride to Phenyloxazoline : Benz-2-chloroethylamide.—A solution of redistilled 2-phenyloxazoline (5·0 g.) in anhydrous alcohol (20 c.c.) was saturated at 5° with anhydrous hydrogen chloride; a solid first separated which redissolved as more hydrogen chloride was passed in. After standing for 2 hours, the solvent was pumped off at 20°, and the residue (5·7 g.; m. p. 98°, softening at 70—80°) crystallised from aqueous methyl alcohol; benz-2-chloroethylamide separated in colourless prisms, m. p. 106° (Found : N, 7·5; Cl, 19·4. Calc. for $C_9H_{10}ONCl$: N, 7·6; Cl, 19·3%). A solution of 2-phenyloxazoline (5·0 g.) in anhydrous ether (50 c.c.) and anhydrous alcohol (3·0 c.c.), saturated with hydrogen chloride and kept for 5 hours at 4°, in the same manner gave 3·5 g. of recrystallised benz-2-chloroethylamide, m. p. 106—108°, with the same analytical figures.

Ethyleneimine (cf. Gabriel and Stelzner, *loc. cit.*).—2-Bromoethylamine hydrobromide (1100 g.) was added portionwise to a solution of potassium hydroxide (900 g.) in water (2 l.) stirred at < 10°. The stirred mixture was then heated to the b. p., and 550 c.c. of distillate collected; the latter was cooled and poured on to potassium hydroxide (200 g.), and the supernatant oil separated and dried overnight with fresh potassium hydroxide (100 g.). The ethyleneimine thus obtained was kept over sodium wire and then distilled from fresh sodium wire; yield 144 g., b. p. 55°.

Benzoylethyleneimine (cf. Gabriel and Stelzner, *loc. cit.*).—Ethyleneimine (10·3 g.) was added to ice-water (200 g.) and the solution stirred rapidly at < 0°. Sodium hydrogen carbonate (20 g.) was added, and then benzoyl chloride (23 g.) added portionwise during 30 minutes, the temperature of the mixture at no time being allowed to exceed 0°. Stirring at this temperature was continued for a further 1 hour, the mixture allowed to attain room temperature, and the layer of benzoylethyleneimine (24·5 g.) separated; this was an oil, f. p. 5° (Found : C, 72·9; H, 6·1; N, 9·3. Calc. for C_9H_9ON : C, 73·4; H, 6·1; N, 9·5%). By separating the solid from the partially frozen material the m. p. was raised to 8—9°; the m. p. of a mixture (50 : 50) of benzoylethyleneimine and 2-phenyloxazoline was < − 12°.

Reaction of Benzoylethyleneimine with Aqueous Hydrochloric Acid.—Benzoylethyleneimine (20 g.; m. p. 8°) was cooled in an ice-bath, ice-cold N-hydrochloric acid (300 c.c.) added, and the solution vigorously shaken; an immediate exothermic reaction developed with separation of benz-2-chloroethylamide. After 15 minutes this was collected, washed with water, and dried; yield 18·1 g. (72·5%), m. p. 102—104° (Found : N, 7·8; Cl, 19·0. Calc. for $C_9H_{10}ONCl$: N, 7·6; Cl, 19·3%). Crude benzoylethyleneimine, m. p. 5°, gave the same yield (72·5%) of the amide.

Thermal Isomerisation of Benzoylethyleneimine.—The crude product from the benzoylation of ethyleneimine was collected in ether, the ethereal extract dried ($MgSO_4$), the ether removed, and the residue distilled *as rapidly as possible*. The distillate, b. p. 128—129°/15 mm. (20 g.), could not be induced to crystallise in an ice–salt bath. Treatment with ice-cold hydrochloric acid in the above manner yielded only 5·9 g. of benz-2-chloroethylamide, m. p. 102—104° (23%); this distillate corresponds to a mixture of *ca.* 70% of phenyloxazoline and *ca.* 30% of benzoylethyleneimine.

Crude (m. p. 5°) benzoylethyleneimine was heated for x hours at the stated temperature and then treated in the same manner with N-hydrochloric acid. The yields of benz-2-chloroethylamide (y%) were :

Temp. 116°.

Time, x hrs.	0	½	1	1½	2	2½	3½
Yield, y %	75	70	64	58	42	28	(gum)

Temp. 55°.

Time, x hrs.	0	1	3	6	24	48	72
Yield, y %	73	72	71	69	66	48	29

Addition of Hydrogen Sulphide to 2-Phenyloxazoline : N-(2-Hydroxyethyl)thiobenzamide.—2-Phenyloxazoline (40 g.) was added to an alcoholic solution of ammonium sulphide (obtained by dissolution of 20 g. of ammonia and then 30 g. of hydrogen sulphide in 200 c.c. of methyl alcohol), and the solution kept in a closed bottle at 30° with occasional shaking for 8 days. The solvent was pumped off and water added to the residue; the solid was collected (51 g.; m. p. 88—92°) and recrystallised from aqueous methyl alcohol, *N-(2-hydroxyethyl)thiobenzamide* (38 g.) being obtained in colourless needles, m. p. 94°. For analysis a sample was recrystallised from the same solvent and obtained in slender colourless prisms, m. p. 96° [Found : C, 60·0; H, 6·2; N, 7·9; S, 17·8; *M* (Rast), 193. $C_9H_{11}ONS$ requires C, 59·7; H, 6·1; N, 7·7; S, 17·7%; *M*, 181]. The compound gave no coloration with sodium nitroprusside in dilute alcoholic solution and was insoluble in dilute hydrochloric acid.

Benzylation of N-(2-Hydroxyethyl)thiobenzamide.—The foregoing compound (40 g.; obtained from the

addition of hydrogen sulphide to 2-phenyloxazoline) was dissolved in a solution of sodium (6·0 g.) in anhydrous ethyl alcohol (250 c.c.), and then benzyl chloride (31·8 c.c.) added. After being kept for 1 hour at room temperature the solution was refluxed for a further 1 hour, alcohol (*ca.* 170 c.c.) distilled off, excess of water added, and the mixture extracted with ether. The ethereal extract (*A*) was shaken with 5N-sodium hydroxide, and the aqueous alkaline extract strongly acidified and shaken with ether; this ethereal extract after drying and distillation yielded benzylthiol (14 g.) as a colourless oil, b. p. 82°/13 mm. (Found: S, 25·9. Calc. for C_7H_8S: S, 25·8%), further identified by treatment with 2 : 4-dinitrochlorobenzene and conversion into 2 : 4-dinitrophenyl benzyl sulphide, m. p. 130° alone and in admixture with authentic material (Found: N, 9·8; S, 11·2. Calc. for $C_{13}H_{10}O_4N_2S$: N, 9·7; S, 11·0%). The ethereal layer remaining after extraction with alkali (*A*) was extracted with 5N-hydrochloric acid, the extract basified with sodium hydroxide, and the liberated oil collected in ether. Distillation of the ethereal solution yielded 2-phenyloxazoline (20 g.), b. p. 122—124°/13 mm., m. p. 12° (Found: N, 9·7. Calc.: N, 9·5%); the picrate had m. p. 186° alone and in admixture with authentic material (Found: C, 47·9; H, 3·4; N, 15·1. Calc. for $C_{15}H_{12}O_8N_4$: C, 47·9; H, 3·2; N, 14·9%). The base was further identified by benzoylation in aqueous sodium hydrogen carbonate solution and isolation of 2-benzamidoethyl benzoate; this had m. p. 88—89° alone and in admixture with material obtained by benzoylation of ethanolamine (Found: C, 71·6; H, 5·6; N, 5·3. Calc. for $C_{16}H_{15}O_3N$: C, 71·4; H, 5·6; N, 5·2%).

Ethylation of 2-Hydroxyethylthiobenzamide.—The amide (8·0 g.) was dissolved in a solution of sodium (1·22 g.) in anhydrous ethyl alcohol (50 c.c.), and the solution refluxed with ethyl iodide (7·2 c.c.) for 2 hours; during this time there was copious evolution of ethylthiol. The solvent was distilled off, water added, and the whole extracted with ether; the ethereal extract yielded 2-phenyloxazoline (4·8 g.), b. p. 120—124°/14 mm. (Found: N, 9·9. Calc. for C_9H_9ON: N, 9·5%). The picrate had m. p. 185—186° alone and mixed with authentic material (Found: N, 15·0. Calc. for $C_{15}H_{12}O_8N_4$: N, 14·9%).

Rational Synthesis of N-(2-*Hydroxyethyl*)*thiobenzamide.*—Ethyl thionbenzoate (Matsui, *loc. cit.*; Delépine, *loc. cit.*) (5·0 g.) and ethanolamine (20 g.) were heated together on the water-bath for ½ hour, the mixture diluted with water, and the precipitate (2·9 g.; m. p. 70—76°) collected. Recrystallisation twice from aqueous methyl alcohol yielded *N*-(2-hydroxyethyl)thiobenzamide in colourless needles, m. p. 94—96° alone and mixed with the material obtained by addition of hydrogen sulphide to phenyloxazoline (Found: N, 8·0; S, 17·8. Calc. for $C_9H_{11}ONS$: N, 7·7; S, 17·7%). This compound gave no coloration with sodium nitroprusside.

S-*Benzyl*-N-iso*propylthiobenzamide.*—This compound was prepared in order to determine the stability of an *NS*-disubstituted thioiminoether. Ethyl thionbenzoate (29·2 g.) was added to *iso*propylamine (41·5 g.) at < 0°, and the mixture gently heated on the water-bath for 1½ hours. Excess of amine was distilled off, water added to the residue, and the precipitated oil collected in ether; distillation of the product gave N-iso*propylthiobenzamide* (18·8 g.) as a viscid yellow oil, b. p. 182—186°/13 mm., which solidified on standing to a mass of yellow crystals, m. p. 53—55° (Found: N, 7·6; S, 18·1. $C_{10}H_{13}NS$ requires N, 7·8; S, 17·9%).

The foregoing thio-amide (18·6 g.) was added to a solution of sodium (2·4 g.) in anhydrous ethyl alcohol (50 c.c.); benzyl chloride (13·3 g.) was added, and the mixture refluxed on the water-bath for 4 hours. The alcohol was distilled away, the residue diluted with water, and the precipitated oil collected in ether. The ethereal solution (*X*) was extracted with dilute sodium hydroxide; acidification of the alkaline layer and ether extraction did not yield any benzylthiol. Distillation of the dried ethereal solution (*X*) gave S-*benzyl*-N-iso*propylthiobenzamide* (27·6 g.) as a viscous yellow oil, b. p. 196—202°/12 mm., which could not be induced to solidify (Found: N, 5·3; S, 11·9. $C_{17}H_{19}NS$ requires N, 5·2; S, 11·9%). The *picrate* crystallised from aqueous alcohol in yellow prisms, m. p. 112° (Found: N, 11·3; S, 6·2. $C_{23}H_{22}O_7N_4S$ requires N, 11·2; S, 6·4%).

S-Benzyl-*N*-*iso*propylthiobenzamide (2·0 g.) was refluxed with 2N-hydrochloric acid (20 c.c.) for 9 hours. The reaction mixture (*A*) was extracted with ether, and the ethereal extract (*B*) shaken with dilute sodium hydroxide; acidification of the aqueous alkaline layer and ether extraction yielded a small amount of benzylthiol (0·1 g.), identified by conversion into 2 : 4-dinitrophenyl benzyl sulphide, m. p. and mixed m. p. 130°. The ethereal solution (*B*) on drying and distillation of the ether left a residual oil (1·4 g.) which solidified on keeping; crystallisation of this from methyl alcohol yielded benzyl thiolbenzoate in colourless prisms, m. p. 42° alone and in admixture with authentic material obtained by benzoylation of benzylthiol (Found: C, 74·0; H, 5·6; S, 14·2. Calc. for $C_{14}H_{12}OS$: C, 73·7; H, 5·3; S, 14·0%). The aqueous acid liquors (*A*) were cooled, basified with 10N-sodium hydroxide, and extracted with benzene (5 c.c.). Addition of a hot benzene solution of picric acid to the dried benzene extract yielded *iso*propylamine picrate in yellow prisms, m. p. 150° alone and mixed with authentic material.

Benzyl-*N*-*iso*propylthiobenzamide (5·0 g.) was refluxed with alcohol (30 c.c.) and 5N-sodium hydroxide (10 c.c.) for 6 hours. After removal of the alcohol the product was collected in ether; removal of solvent yielded benzyl thiolbenzoate (2·0 g.), m. p. and mixed m. p. 40—42°.

S-Benzyl-*N*-*iso*propylthiobenzamide was recovered unchanged after refluxing for 10 hours with 0·5N-sodium hydroxide.

Addition of Hydrogen Sulphide to Benzoylethyleneimine: 2-Benzamidoethylthiol.—Benzoylethyleneimine (22 g.) was added to an alcoholic solution of ammonium sulphide (12 g. of ammonia and 18 g. of hydrogen sulphide dissolved in 150 c.c. of methyl alcohol). An immediate exothermic reaction developed (contrast the slow reaction with phenyloxazoline); after 20 hours at room temperature the solvent was removed under reduced pressure at 40°. Recrystallisation of the drained residue (15 g.; m. p. 66—70°) from benzene–ligroin gave 2-*benzamidoethylthiol* in colourless leaves, m. p. 70—71° [Found: C, 59·4; H, 6·0; N, 8·0; S, 17·8; *M* (Rast), 190. $C_9H_{11}ONS$ requires C, 59·7; H, 6·1; N, 7·7; S, 17·7%; *M*, 181]. The compound gave a powerful purple coloration with sodium nitroprusside; the mixed m. p. with *N*-(2-hydroxyethyl)thiobenzamide (m. p. 96°; obtained by addition of hydrogen sulphide to phenyloxazoline) was 36—44°.

Benzylation of 2-Benzamidoethylthiol: Benzyl 2-Benzamidoethyl Sulphide.—2-Benzamidoethylthiol (10·1 g.) was added to a solution of sodium (1·3 g.) in anhydrous ethyl alcohol (50 c.c.). After ½ hour,

benzyl chloride (7·0 g.) was added, the solution kept for 1 hour and refluxed for a further 1 hour, the solvent distilled off, and excess of water added. The precipitate was collected and recrystallised from aqueous methyl alcohol, benzyl 2-benzamidoethyl sulphide being obtained in colourless needles, m. p. 76—78°; these, after recrystallisation, had m. p. 79° alone and in admixture with authentic material prepared (see below) by benzylation and then benzoylation of 2-aminoethylthiol (Found: N, 5·4; S, 11·6. Calc. for $C_{16}H_{17}ONS$: N, 5·2; S, 11·8%).

Benzyl 2-Aminoethyl Sulphide.—This compound was prepared by Michels (*loc. cit.*) by the interaction of 2-phthalimidoethylthiol and benzyl chloride followed by hydrolysis; owing to the difficulty in removing the phthaloyl residue the following more convenient route was employed. 2-Aminoethylthiol (7·7 g.; Mills and Bogert, *loc. cit.*; cf. Gabriel, *Ber.*, 1897, **30**, 2497) was dissolved in a solution of sodium (2·3 g.) in anhydrous alcohol (60 c.c.), and then benzyl chloride (10 c.c.) added. After the abatement of the exothermic reaction the mixture was refluxed for 1 hour, the solvent distilled off, water added, and the whole extracted several times with ether. The ethereal solution was extracted with 5N-hydrochloric acid (3 × 25 c.c.), and the aqueous acid extract basified with ammonia and extracted with ether. Distillation of the latter yielded benzyl 2-aminoethyl sulphide as a colourless oil (10·2 g.), b. p. 150—152°/13 mm. (Found: N, 8·4. Calc. for $C_9H_{13}NS$: N, 8·4%). This (1·67 g.) was refluxed with phthalic anhydride (1·48 g.) and glacial acetic acid (10 c.c.) for ¼ hour, and the boiling solution diluted to incipient crystallisation with hot water; benzyl 2-phthalimidoethyl sulphide separated in colourless glittering plates (1·65 g.), m. p. 76—78° alone and in admixture with authentic material obtained by benzylation of 2-phthalimidoethylthiol (Michels, *loc. cit.*) (Found: N, 4·8; S, 10·8. Calc. for $C_{17}H_{15}O_2NS$: N, 4·7; S, 10·8%). Benzoylation of the amine in presence of aqueous sodium hydrogen carbonate yielded benzyl 2-benzamidoethyl sulphide in colourless needles, m. p. 79° alone and in admixture with the material obtained by the benzylation of 2-benzamidoethylthiol (see above) (Found: N, 5·5; S, 11·5. Calc. for $C_{16}H_{17}ONS$: N, 5·2; S, 11·8%).

2-(*Acetylsulphanilamido*)*ethyl Bromide.*—Sodium carbonate (7·0 g.) was added to an ice-cold stirred solution of 2-bromoethylamine hydrobromide (10 g.) in water (25 c.c.) and acetone (40 c.c.), and then acetylsulphanilyl chloride (11·0 g.) was added portionwise. Stirring was continued for a further ½ hour, water (50 c.c.) added, and the precipitate (13·1 g.) collected; recrystallisation from aqueous methyl alcohol yielded 2-(*acetylsulphanilamido*)*ethyl bromide* in colourless needles, m. p. 168—170° (Found: N, 9·0; Br, 24·9; S, 10·4. $C_{10}H_{13}O_3N_2BrS$ requires N, 8·7; Br, 24·9; S, 10·0%).

Acetylsulphanilylethyleneimide.—A solution of the foregoing compound (31·7 g.) in water (200 c.c.) and 5N-sodium hydroxide (100 c.c.) was kept at 20° for ½ hour, by which time a heavy precipitate (19 g.) had separated. The *imide* was collected, washed with water, and dried in a vacuum; a sample crystallised from water in colourless needles, m. p. 116—118° (Found: N, 11·7; S, 13·0. $C_{10}H_{12}O_3N_2S$ requires N, 11·7; S, 13·3%).

2-(*Acetylsulphanilamido*)*ethylthiol.*—Acetylsulphanilylethyleneimide (19 g.) was added to a methanolic solution of ammonium sulphide (10 g. ammonia, 16 g. hydrogen sulphide in 120 c.c. methyl alcohol), and the solution kept at room temperature for 48 hours. The solvent was pumped off, water added, and the solid (17 g.; m. p. 120°) collected; crystallisation from aqueous methyl alcohol yielded 2-(*acetylsulphanilamido*)*ethylthiol* in pale pink prisms, m. p. 126—128° (Found: N, 10·5; S, 23·5. $C_{10}H_{14}O_3N_2S_2$ requires N, 10·2; S, 23·4%). The compound gave an intense purple coloration with sodium nitroprusside.

2-*Sulphanilamidoethylthiol Hydrochloride.*—A solution of the foregoing acetyl compound (4·0 g.) in alcohol (40 c.c.) and 10% w/w alcoholic hydrogen chloride (60 c.c.) was refluxed for 1½ hours. After the solvent had been pumped off, 2-*sulphanilamidoethylthiol hydrochloride* (2·6 g.) separated in small colourless prisms, m. p. 210—212° (Found: N, 10·6; Cl, 13·5; S, 23·5. $C_8H_{12}O_2N_2S_2$,HCl requires N, 10·4; Cl, 13·2; S, 23·8%). The free base was an oil which could not be induced to crystallise.

Benzeneazoacetoacetic Acid (cf. Bülow and Neber, *Ber.*, 1912, **45**, 3732).—A solution of aniline (91 c.c.) in 5N-hydrochloric acid (500 c.c.) was diazotised at 0—5° with a solution of sodium nitrite (73 g.) in water (250 c.c.); after a further 10 minutes' stirring, saturated sodium acetate solution was added until the solution was no longer acid to Congo-red. This solution was added slowly to a stirred solution of ethyl acetoacetate (127 c.c.) and sodium acetate (120 g.) in water (200 c.c.) and alcohol (750 c.c.), the temperature being kept below 10°. After the addition, the reaction mixture was stirred for a further ½ hour at 5—10° and then for 1½ hours at room temperature, diluted with water (1000 c.c.), and the ethyl benzeneazoacetoacetate (229 g.), m. p. 76—78°, filtered off and dried at 20°.

5N-Sodium hydroxide (120 c.c.; 0·6 mol.) was added to a solution of the foregoing ester (50 g.; 0·21 mol.) in alcohol (500 c.c.), and the mixture kept at room temperature for 20 hours. The yellow felted needles of sodium benzeneazoacetoacetate, m. p. 210—222°, which separated were collected and washed with alcohol (Found, in material dried at 120°: Na, 9·8. Calc. for $C_{10}H_9O_3N_2Na$: Na, 10·1%). The sodium salt was dissolved in boiling water (1 l.), and the solution acidified with hydrochloric acid, benzeneazoacetoacetic acid (37 g.) separating in fine yellow needles, m. p. 164° (cf. Bülow, *Ber.*, 1899, **32**, 197).

Benzeneazoacetoacetylethyleneimide.—Benzeneazoacetoacetic acid (20 g.) was dissolved in chloroform (60 c.c.), the solution cooled in an ice-bath, and powdered phosphorus pentachloride (25 g.) added portionwise. After standing at room temperature overnight, the solvent was pumped off at 20°, xylene (40 c.c.) added, and this pumped off at 30°. The residue was boiled with benzene (100 c.c.) and the filtered solution chilled; *benzeneazoacetoacetyl chloride* (12 g.) separated in golden brown plates, m. p. 122—124°. A sample crystallised from benzene–ligroin in golden plates, m. p. 125° (Found: N, 12·8; Cl, 16·0. $C_{10}H_9O_2N_2Cl$ requires N, 12·5; Cl, 15·8%).

The foregoing acid chloride (17·2 g.) was added portionwise to a stirred solution of ethyleneimine (17 c.c.) in water (80 c.c.) at 10°. After stirring at this temperature for a further ½ hour the *benzeneazoacetoacetylethyleneimide* (9·3 g.; m. p. 88—90°) was collected and washed with water; a sample separated from benzene–ligroin in golden needles with the same m. p. (Found: C, 61·9; H, 5·6; N, 18·4. $C_{12}H_{11}O_2N_3$ requires C, 62·3; H, 5·6; N, 18·2%).

Addition of Hydrogen Sulphide to Benzeneazoacetoacetylethyleneimide: Formation of (IX) *or* (XI).—The foregoing imide (11·1 g.) was added to an alcoholic solution of ammonium sulphide (7 g. of ammonia

and 14 g. of hydrogen sulphide in 100 c.c. of methyl alcohol); after the initial exothermic reaction had subsided (compare reaction with benzoylethyleneimine and contrast reaction with phenyloxazoline) the mixture was kept at room temperature for 24 hours and the crystalline precipitate (7·5 g.; m. p. 146—150°) collected. Recrystallisation from chloroform–methanol yielded a *compound* (6·0 g.) in fine yellow needles, m. p. 164—166°, which gave no coloration with sodium nitroprusside (Found: C, 54·5; H, 5·4; N, 16·0; S, 12·3. $C_{12}H_{15}O_2N_3S$ requires C, 54·3; H, 5·7; N, 15·85; S, 12·1%). The substance was insoluble in cold alcoholic sodium hydroxide. It was recovered unchanged (m. p. and mixed m. p.) after refluxing with dilute alcoholic sodium hydroxide and after standing for 30 days with 12% alcoholic hydrogen chloride or 5N-alcoholic ammonia.

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389. *The Synthesis of 7-Amino-alloxazines and -isoalloxazines.*

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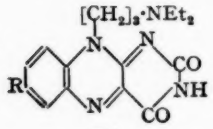
The application of Piloty's synthesis (*Annalen*, 1904, **333**, 44) of 7-aminoalloxazine (IV), from violuric acid and *m*-phenylenediamine, to secondary-tertiary-*m*-diamines has given 7-*dialkylamino*iso*alloxazines* of type (VI), identical with the condensation products of the appropriately alkylated 1 : 2 : 4-triaminobenzenes and alloxan. Measurements of absorption spectra and chemical examination of the product show that the action of violuric acid on *N*-methyl-*m*-phenylenediamine leads to a mixture of the *alloxazine* (VII) and the iso*alloxazine* (VIII).

IN view of their possible microbiological activity, as analogues of riboflavin, various *iso*alloxazines with simple dialkylaminoalkyl groups in the 9-position have recently been synthesised (King and Acheson, *J.*, 1946, 682; Neeman, *ibid.*, p. 811; Adams, Weisel, and Mosher, *J. Amer. Chem. Soc.*, 1946, **68**, 883; Kipnis, Weiner, and Spoerri, *ibid.*, 1947, **69**, 799; Hippchen, *Ber.*, 1947, **80**, 263). In general, these *iso*alloxazines are *benz*-chloro-, -nitro-, -methoxyl- or -methyl derivatives, which have been obtained by condensing in acid solution the corresponding *o*-phenylenediamines with alloxan. *iso*Alloxazines with amino-groups in the benzene nucleus have not so far been described; as already indicated (King and Acheson, *loc. cit.*), 2 : 4-diamino-γ-diethylaminopropylaniline failed, under the usual conditions, to give the expected 6-amino*iso*alloxazine (I; R = NH_2). Certain aminoalloxazines, on the other hand, are already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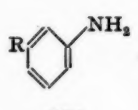
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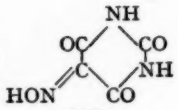
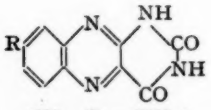
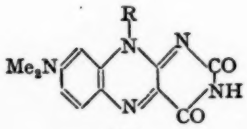
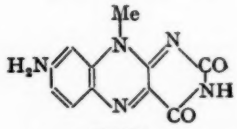

(III.)


(IV; R = NH_2.)
(VII; R = NHMe.)
(IX; R = NMe_2.)

(V.)


(VI.)


(VIII.)

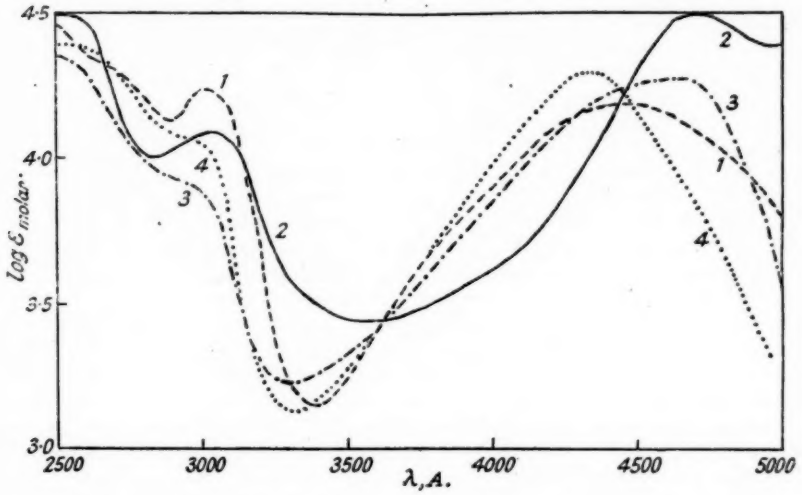
known, having been prepared by Piloty (*Annalen*, 1904, **333**, 44) from *m*-phenylenediamine (II; R = NH_2) and violuric acid (III) or its 1 : 3-dimethyl derivative. The present communication reports the extension of this synthesis to several amino*iso*alloxazines.

Alloxazine formation from violuric acid and a *m*-phenylenediamine depends on the presence in the latter of an activated position *ortho* to the condensing amino-group. From the amine (II; R = NH_2), in which both the 2- and the 6-position are free, either the 5- or the 7-amino-alloxazine may result, but, as recognised by Piloty (*loc. cit.*), the compound most likely to be obtained is the 7-amino-derivative (IV; R = NH_2). Ganapati (*J. Indian Chem. Soc.*, 1938, **15**, 77) attempted to resolve this point by applying the *o*-phenylenediamine–alloxan synthesis to 1 : 2 : 4-triaminobenzene, but the properties of the product (probably a mixture of 6- and 7-aminoalloxazine) and of Piloty's aminoalloxazine, both of which are sparingly soluble red powders with high decomposition points, rendered their comparison inconclusive.

The 7-amino-structure assigned to Piloty's *m*-phenylenediamine–violuric acid condensate now

appears to be confirmed by analogy with the results of the following experiments. 3-*Dimethylamino*-β-*diethylaminoethylaniline* (V; R = H) reacted with violuric acid in hot alcoholic solution giving 7-dimethylamino-9-β-diethylaminoethyl*iso*alloxazine (VI; R = $[CH_2]_2 \cdot NEt_2$), which separated as a tetrahydrated *violurate*. Its constitution as the 7-dimethylamino-compound was proved by a synthesis of the base from alloxan and 2-amino-5-dimethylamino-β-diethylaminoethylaniline (V; R = NH_2) in boric–acetic acid solution. The complete identity of both products was established through the above violurate and also by means of the common *picrate*.

Of the materials required for these syntheses, 3-dimethylamino-β-diethylaminoethylaniline (V; R = H) was prepared from 3-*dimethylamino*-p-*toluenesulphonanilide* by alkylation with diethyl-β-chloroethylamine, the resulting oily sulphonamide being hydrolysed by cold sulphuric acid. The triaminobenzene (V; R = NH_2) used in the alloxan synthesis is the reduction product of 2-*nitro*-5-*dimethylamino*-β-*diethylaminoethylaniline* (V; R = NO_2) which was obtained by heating 3 : 4-dinitrodimethylaniline with β-diethylaminoethylamine, the labile 3-nitro-group being displaced (cf. Forster and Coulson, *J.*, 1922, **121**, 1988; Romburgh, *Rec. Trav. chim.*, 1923, **42**, 804). For the preparation of the necessary dinitro-base, direct nitration of 3-nitro-*N*-dimethylaniline (Romburgh, *ibid.*, 1887, **6**, 250; Swann, *J.*, 1920, **3**) was found to be preferable



to the method of Hodgson and Smith (*ibid.*, 1931, 1508), using nitrous acid as nitrating agent, which gives a mixture of products.

The use of a secondary-tertiary amine in the Piloty synthesis admits only of the formation of alloxazines, but from a primary-secondary-*m*-diamine, *e.g.*, *N*-methyl-*m*-phenylenediamine (II; R = NHMe), condensation with violuric acid may give either an alloxazine (VII) or an *iso*alloxazine (VIII). When the experiment was tried, a microcrystalline substance was obtained which was at first believed to be homogeneous. The constitution of this product, whether alloxazine or *iso*alloxazine, was thought to be ascertainable by comparison of its ultra-violet absorption with the spectra of reference compounds of established structure. For this purpose the orange-red microcrystalline 7-*dimethylaminoalloxazine* (IX) was synthesised from *m*-amino-*N*-dimethylaniline and violuric acid, and the corresponding 7-*dimethylamino*-9-*methyl*iso*alloxazine* (VI; R = Me), a carmine powder, similarly prepared from *m*-methylamino-*N*-dimethylaniline, the latter being obtained from 3-dimethylamino-*p*-toluenesulphonanilide by methylation and hydrolysis.

The absorption spectra of these two reference compounds, the alloxazine (IX) (Curve 1) and the *iso*alloxazine (VI; R = Me) (Curve 2), are shown in the figure: although not in marked contrast, they exhibit an observable difference throughout the whole wave band examined. On plotting the data obtained for the *m*-aminomethylaniline–violuric acid product, the resulting curve (3) was found to lie between those of the two reference compounds, and it became apparent that the material was heterogeneous. Repeated extraction of the red-brown condensate with dilute hydrochloric acid, which was designed to remove the more basic *iso*alloxazine, left an orange solid having a spectrum (Curve 4) approximating closely to that of the alloxazine. In

view of the colour difference between the reference compounds the change of colour to orange on washing with acid is significant.

The absorption curves of the 7-amino-alloxazine and -*iso*alloxazine differ appreciably from those recorded for the 9-diethylaminoalkyl*iso*alloxazines and for riboflavin by Adams, Weisel, and Mosher (*loc. cit.*). In addition to general displacement of the curves towards the lower frequencies, the absorption maxima at *ca.* 3,500 A. exhibited by riboflavin and the compounds of Adams *et al.* have disappeared.

The effect of nitrous acid on the product in question provided further evidence of its heterogeneous character. Diazotisation in sulphuric acid solution precipitated the sparingly soluble 7-N-*nitrosomethylaminoalloxazine*. This was removed, and the filtrate coupled with alkaline β-naphthol, whereupon the presence of the amino*iso*alloxazine was demonstrated by the formation of a deep olive-green *azo-dye*. Diazotisation of 7-aminoalloxazine under the same conditions gave a clear solution which afforded a very similar azo-β-naphthol *compound*. From the relative proportions of these derivatives obtained in the two experiments the percentage of alloxazine to *iso*alloxazine in the mixture is calculated as approximately 40/60. From the action of violuric acid on *m*-amino-β-diethylaminoethylaniline, which was prepared from *3'-nitro*-p-*toluenesulphon*-(β-*diethylaminoethyl*)*anilide* by removal of the tosyl group and reduction of the resulting *nitro-amine*, a crystalline *violurate* was isolated. This may have contained alloxazine or *iso*alloxazine, but its constitution was not further investigated.

The high proportion of *iso*alloxazine in the mixed product of the diamine–violuric acid condensation is to be expected from the probable course of the reaction, *i.e.*, preliminary addition at the 4- or 6-carbonyl of the pyrimidine followed by ring-closure between the oximino-group and the activated 6-position in the benzene ring. With amino-groups of different basicities, *e.g.*, NH_2 and NHMe, reaction with the more basic centre, *i.e.*, NHMe, would predominate, leading to a higher proportion of *iso*alloxazine. Condensation of the oximino-group with an activated position in the aromatic nucleus as the preliminary step is very improbable, since the intermediate would be analogous to the so-called Kuhling products obtained when the condensation of *o*-diamines with alloxan is carried out in the absence of acid, and these are known to be extremely resistant to cyclisation (Tishler, Wellman, and Ladenburg, *J. Amer. Chem. Soc.*, 1945, **67**, 2165).

Attempts have been made by Ganapati (*loc. cit.*) to extend the Piloty synthesis to other *m*-substituted anilines, but without success, from which he concludes that the *m*-amino-group is specific for this reaction. It is evident, however, that the degree of activation in the aromatic nucleus is the important factor, since from 4-aminoveratrole and violuric acid in acetic acid solution, it has been possible to synthesise, though not in a spectroscopically pure condition, 6 : 7-*dimethoxyalloxazine*. The nature of the product has been demonstrated by an independent synthesis from 4 : 5-diaminoveratrole and alloxan.

In addition to the above 7-amino-compounds, 7-chloro-9-β-diethylaminoethyl- and 7-chloro-9-γ-diethylaminopropyl-*iso*alloxazine have been synthesised by the alloxan method, and characterised by *picrates* and hydrated *hydrochlorides*. The necessary triamines were prepared by the action of 2 : 4-dichloronitrobenzene on the diethylaminoalkylamines, the resulting 2-nitro-5-chloroamines, which were analysed as *hydrochlorides* and *picrates*, being reduced by the catalytic method immediately before condensation.

Experimental.

3-Dimethylamino-p-toluenesulphonanilide.—*m*-Nitrodimethylaniline (15·3 g.) was reduced in methanol solution (50 c.c.) over Raney nickel, and after filtration from catalyst the resulting diamine was treated with *p*-toluenesulphonyl chloride (18·5 g.). The mixture was heated on a steam-bath for 20 minutes, diluted with water, and basified with ammonia. The precipitated *sulphonamide* crystallised from ethanol in colourless prisms. m. p. 156° (16 g., 68%) (Found : C, 62·0; H, 5·8; S, 10·7. $C_{15}H_{18}O_2N_2S$ requires C, 62·1; H, 6·2; S, 11·0%).

3-Dimethylamino-β-diethylaminoethylaniline (V; R = H).—Diethyl-β-chloroethylamine (4·2 g.) and 3-dimethylamino-*p*-toluenesulphonanilide (9·0 g.) were added to a solution of sodium (0·72 g.) in ethanol (50 c.c.). After refluxing on a steam-bath for 6 hours, the solvent was evaporated, and the residue treated with water and shaken with chloroform. Evaporation of the chloroform layer gave the alkylated sulphonanilide as an oil which neither solidified nor formed crystalline derivatives. It was therefore hydrolysed with sulphuric acid (100 g. of 94%) at room temperature, the brown solution being diluted with ice-water and basified after 20 hours to give *3-dimethylamino-β-diethylaminoethylaniline* as a pale yellow oil, b. p. 115—117° (bath temp.)/0·03 mm. (4·45 g., 61%) (Found : C, 71·5; H, 10·7. $C_{14}H_{25}N_3$ requires C, 71·5; H, 10·6%). A *monopicrate* separated from aqueous ethanol in very deep red prisms, m. p. 133° (Found : C, 51·4; H, 6·1; N, 18·6. $C_{14}H_{25}N_3,C_6H_3O_7N_3$ requires C, 51·7; H, 6·0; N, 18·1%). The *dipicrate* crystallised from ethanol as a yellow powder, m. p. 143—144° (decomp.) (Found : C, 44·9; H, 4·6. $C_{14}H_{25}N_3,2C_6H_3O_7N_3$ requires C, 45·0; H, 4·5%).

3 : 4-*Dinitro*-N-*dimethylaniline*.—The nitration of 3-nitrodimethylaniline following the directions of Hodgson and Smith (*loc. cit.*) gave only 26% of the desired 3 : 4-dinitro-compound and much 3-nitro-*N*-nitroso-*N*-methylaniline. Direct nitration (cf. Romburgh, *loc. cit.*) was accomplished by adding the finely powdered amine (4 g.) to dilute nitric acid (80 c.c. of 20%). After vigorous shaking for 10 minutes the mixture was diluted with water, and the precipitate collected and dissolved in boiling *n*-propanol. On cooling, 3 : 4-dinitrodimethylaniline (2·07 g., 41%), m. p. 178—179°, separated in yellow needles. Dilution of the mother-liquor with water precipitated 2 : 5-dinitrodimethylaniline, crystallising from ethanol in scarlet prisms (0·7 g., 14%), m. p. 112°.

2-*Nitro*-5-*dimethylamino*-β-*diethylaminoethylaniline* (V, R = NO_2).—3 : 4-Dinitrodimethylaniline (3·84 g., 1 mol.), β-diethylaminoethylamine (3·2 g., 1·5 mols.), and anhydrous sodium acetate (4 g.) were heated in an oil-bath, a vigorous reaction occurring. After 6 hours at 140—160°, the mixture was cooled, and acidified with dilute acid, the aqueous solution then being washed with ether. Addition of alkali gave a product which, when isolated, distilled at 195—205° (bath temp.)/0·1 mm. as a light brown oil (3·9 g., 77%). This consisted of the *nitro-amine* (V; R = NO_2), which crystallised in yellow-brown prisms, m. p. 45—46° (Found : N, 20·3. $C_{14}H_{24}O_2N_4$ requires N, 20·0%). The *picrate* separated from aqueous ethanol in yellow diamond-shaped plates, m. p. 171° (decomp.) (Found : C, 46·8; H, 5·4; N, 18·6. $C_{14}H_{24}O_2N_4,C_6H_3O_7N_3$ requires C, 47·1; H, 5·3; N, 19·3%).

7-*Dimethylamino*-9-β-*diethylaminoethyl*isoalloxazine (VI; R = $[CH_2]_2{\cdot}NEt_2$).—(i) On mixing hot solutions of 3-dimethylamino-β-diethylaminoethylaniline (V; R = H) (2·75 g., 1 mol.) in ethanol (10 c.c.) and of violuric acid (1·84 g., 1 mol.) in water (20 c.c.), a purple colour appeared, rapidly changing to crimson. After 1 hour on a steam-bath the mixture was evaporated under reduced pressure, and the product treated with boiling ethanol (20 c.c.). The residue of *iso*alloxazine violurate (2·35 g., 69% calc. on violuric acid), m. p. 265° (decomp.), crystallised from its deep crimson aqueous solution as red-brown hair-like needles of the *tetrahydrate* (Found : C, 45·4; H, 5·7; N, 22·4. $C_{18}H_{24}O_2N_6,C_4H_3O_4N_3,4H_2O$ requires C, 45·1; H, 6·0; N, 21·5%. Found, after drying at 120° in a vacuum : C, 50·5; H, 5·3; N, 24·3; loss, 10·2. $C_{18}H_{24}O_2N_6,C_4H_3O_4N_3,\frac{1}{2}H_2O$ requires C, 50·6; H, 5·4; N, 25·1; loss, 10·8%. Found, after drying at 150° in a vacuum : C, 51·1; H, 5·5; loss, 11·6. $C_{18}H_{24}O_2N_6,C_4H_3O_4N_3$ requires C, 51·5; H, 5·3; loss, 12·3%). The hydrated *hydrochloride*, which was purified by precipitation with ether from methanolic hydrogen chloride, formed a bright red microcrystalline powder, very soluble in water, m. p. 290° (decomp.) (Found, after drying at 100° in a vacuum : C, 53·0; H, 6·5; N, 19·8; Cl, 8·3. $C_{18}H_{24}O_2N_6,HCl,H_2O$ requires C, 52·6; H, 6·6; N, 20·5; Cl, 8·7%). The *iso*alloxazine *picrate* crystallised from aqueous alcohol in dull red minute needles, m. p. 242° (decomp.) (Found, after drying at 120° in a vacuum : C, 48·9; H, 4·9; N, 21·2. $C_{18}H_{24}O_2N_6,C_6H_3O_7N_3$ requires C, 49·2; H, 4·6; N, 21·5%).

(ii) 2-Nitro-5-dimethylamino-β-diethylaminoethylaniline (V; R = NO_2) (0·9 g., 1 mol.) was reduced in acetic acid (25 c.c.) over palladised charcoal catalyst, and the filtered solution of the amine added to warm acetic acid (30 c.c.) containing alloxan monohydrate (0·6 g., 1·17 mols.) and boric acid (0·9 g.). After 30 minutes at 60°, the deep orange-red solution was evaporated to dryness, and the residue taken up in hot water (15 c.c.). Neutralisation with dilute sodium hydroxide gave the iso*alloxazine* (VI; R = $[CH_2]_2{\cdot}NEt_2$) (0·47 g., 41%), m. p. *ca.* 278° (decomp.). When purified by acidification of its solution in alkali, the base separated as a monohydrate in hair-like carmine needles, m. p. 298—300° (decomp.) (Found : C, 57·5; H, 6·8; N, 23·0. $C_{18}H_{24}O_2N_6,H_2O$ requires C, 57·8; H, 7·0; N, 22·5%. Found, after drying at 200° in a vacuum : C, 59·3; H, 6·5; loss, 2·4. $C_{18}H_{24}O_2N_6,\frac{1}{2}H_2O$ requires C, 59·2; H, 6·8; loss, 2·4%). The *iso*alloxazine was characterised by the picrate, m. p. 242° (decomp.) (Found : C, 48·6; H, 4·8; N, 21·9%), and violurate, m. p. 264° (decomp.) (Found, after drying at 120° in a vacuum : C, 50·4; H, 5·5; loss, 10·5%), already described.

7-*Dimethylaminoalloxazine* (IX).—*m*-Nitro-*N*-dimethylaniline (1 g.) dissolved in ethanol (20 c.c.) was hydrogenated in presence of Raney nickel, and the filtered liquid added to a solution of violuric acid (0·95 g.) in hot water (10 c.c.). After being heated to boiling for 1 hour, the crimson solution had deposited a dark red solid, which was collected next day (yield 1·03 g., 66·5%) and washed sparingly with water and then ethanol. The *alloxazine* (IX) was purified by dissolving it in aqueous methanol containing sodium hydroxide (1½%) and precipitated by the addition of hydrochloric acid to the boiling deep red solution. The orange-red powder then had m. p. 355—357° (decomp.) (Found, after drying at 120° in a vacuum : C, 54·2, 53·7; H, 4·3, 4·7; N, 26·9, 26·7. $C_{12}H_{11}O_2N_5,\frac{1}{2}H_2O$ requires C, 54·1; H, 4·5; N, 26·3%). The ultra-violet spectrum (Curve 1) was determined in N/20-aqueous sodium hydroxide. From more concentrated alkali the *sodio*-derivative separated in brick-red prisms (Found, after drying at 120° in a vacuum : C, 50·2; H, 4·2. $C_{12}H_{10}O_2N_5Na,\frac{1}{2}H_2O$ requires C, 50·0; H, 3·8%).

m-*Methylamino*-N-*dimethylaniline*.—*m*-Dimethylamino-*p*-toluenesulphonanilide (4 g.) and methyl iodide (2 g.) were added to a solution of sodium (0·32 g.) in ethanol (20 c.c.), and the mixture heated under reflux for 7 hours. The oil obtained on evaporation of the alcohol solidified when treated with dilute acid. Crystallisation from water gave 3-p-*toluenesulphonmethylamido*-N-*dimethylaniline hydriodide* (4·3 g., 72%) in colourless needles, m. p. 163° (decomp.) (Found : C, 44·6; H, 5·0; I, 28·2. $C_{16}H_{20}O_2N_2S,HI$ requires C, 44·4; N, 4·9; I, 29·4%). The free base could not be crystallised, and hydrolysis of the sulphonamide was carried out with the salt (3·85 g.), which was mixed with sulphuric acid (15 c.c. of 98%). A vigorous reaction occurred, and after 24 hours the deep blue solution was diluted with ice-water, filtered from iodine, and basified. The methylaminodimethylaniline, a colourless oil (0·7 g., 52%), was identified by analysis of the *dipicrate*, yellow-brown prisms from alcoholic picric acid, m. p. 124° (decomp.) (Found : C, 41·4; H, 3·6. $C_9H_{14}N_2,2C_6H_3O_7N_3$ requires C, 41·4; H, 3·3%).

7-*Dimethylamino*-9-*methyl*isoalloxazine (VI; R = Me).—The *m*-methylaminodimethylaniline (0·45 g.) in ethanol (3 c.c.) was heated with a concentrated aqueous solution of violuric acid (0·47 g.) in a steam-bath for 1½ hours. The iso*alloxazine* (VI; R = Me) which had precipitated from the deep crimson solution was collected and washed with water and ethanol (yield 0·6 g., 74%). The product was dissolved in boiling 1½% aqueous sodium hydroxde, and on neutralisation with dilute hydrochloric acid gave brick-red needles, m. p. 360° (decomp.) (Found, after drying at 120° in a vacuum : C, 57·8; H, 5·1; N, 25·8. $C_{13}H_{13}O_2N_5$ requires C, 57·6; H, 4·8; N, 25·8%). The ultra-violet spectrum in N/7-aqueous sodium hydroxide is shown as Curve 2.

Condensation of m-*Amino*-N-*methylaniline with Violuric Acid.*—*m*-Nitro-*N*-methylaniline (2 g.) was hydrogenated in methanol (20 c.c.) over Raney nickel, and the resulting solution of the diamine treated with violuric acid (2·1 g.) in boiling water (20 c.c.). After an hour's heating on a steam-bath and addition of water (20 c.c.), the dark red solid which had separated (2·06 g., 93%), m. p. 335—337° (decomp.), was collected and dissolved in 1½% aqueous sodium hydroxide. On acidification of the deep red solution the product separated in a gelatinous form; by repeated solution in alkali and reprecipitation, a red-brown solid, m. p. 340—345° (decomp.), was obtained (Found, after drying at 120° in a vacuum : C, 52·4; H, 4·1; N, 27·2. $C_{11}H_9O_2N_5,\frac{1}{2}H_2O$ requires C, 52·4; H, 4·0; N, 27·8%). The ultra-violet spectrum of the material in N/10-sodium hydroxide is represented by Curve 3.

A specimen of the crude product (0·3 g.) was extracted thrice with hot N-hydrochloric acid (total 120 c.c.), and the residue then purified as above. The orange-red powder had m. p. 352—355° (decomp.), and from its ultra-violet spectrum (Curve 4), which was determined in N/10-alkali, it is believed to consist of 7-*methylaminoalloxazine* (VII) (Found : C, 47·1; H, 4·8; N, 24·4. $C_{11}H_9O_2N_5,2H_2O$ requires C, 47·3; H, 4·7; N, 25·1%. Found, after drying at 120° in a vacuum : C, 52·4; H, 3·9; loss, 9·3. $C_{11}H_9O_2N_5,\frac{1}{2}H_2O$ requires C, 52·4; H, 4·0; loss, 9·7%).

A further specimen of the unpurified product (0·2 g.) was dissolved in warm sulphuric acid (4 c.c. of 70%), and after cooling to 0° was treated with 10% aqueous sodium nitrite (1 c.c.), the salt which precipitated on cooling being disregarded. The mixture was left for a time, then diluted with water (25 c.c.), and the 7-*nitrosomethylaminoalloxazine* (0·08 g.), a yellow powder decomposing >300°, collected and washed with water (Found : C, 46·4; H, 3·3; N, 28·8. $C_{11}H_8O_3N_6,\frac{1}{2}H_2O$ requires C, 46·9; H, 3·2; N, 29·9%. Found, after drying at 120° in a vacuum : C, 49·4; H, 3·3. $C_{11}H_8O_3N_6$ requires C, 48·5; H, 2·9%). The filtrate was added to a solution of β-naphthol (0·12 g.) in aqueous sodium hydroxide (30 c.c. of 15%), and after a short time the deep purple solution was neutralised with acetic acid. The precipitated *azo*-compound (0·15 g.), a deep olive-green powder, m. p. 310° (decomp.), was collected and well washed with water and ethanol (Found : C, 56·1; H, 4·2; N, 17·9. $C_{21}H_{14}O_3N_6,3H_2O$ requires C, 55·7; H, 4·4; N, 18·6%. Found, after drying at 150° in a vacuum : C, 60·1; H, 3·8; loss, 8·0. $C_{21}H_{14}O_3N_6,H_2O$ requires C, 60·6; H, 3·8; loss, 8·0%).

When 7-aminoalloxazine (0·2 g.) was diazotised under exactly the above conditions a clear solution was obtained, which gave with alkaline β-naphthol a deep olive-green *azo*-compound (0·23 g.), m. p. 335—338° (decomp.) after sintering *ca.* 275°, dissolving in alkali to a red solution (Found : C, 57·4; H, 4·0; N, 19·1. $C_{20}H_{12}O_3N_6,2H_2O$ requires C, 57·1; H, 3·8; N, 20·0%. Found, after drying at 120° in a vacuum : C, 61·0; H, 3·3; loss, 7·3. $C_{20}H_{12}O_3N_6,\frac{1}{2}H_2O$ requires C, 61·1; H, 3·3; loss, 6·4%).

3′-*Nitro*-p-*toluenesulphon*-(β-*diethylaminoethyl*)*anilide.*—Finely powdered sodamide (1·6 g.) was added during 25 minutes to a well-stirred solution of diethyl-β-chloroethylamine (5·5 g.) and 3′-nitro-*p*-toluenesulphonanilide (10·5 g.) in toluene (200 c.c.). The mixture was slowly heated (1 hour) to 100°, and after 3 hours at 100° was refluxed for a further hour. The solution was then filtered and extracted 4 times with hot 5% hydrochloric acid (total 400 c.c.). Concentration and cooling of the acid extract gave the alkylated sulphonamide *hydrochloride*, which crystallised in colourless silky needles (12 g., 78%), m. p. 182° (Found : C, 53·1; H, 6·0; N, 9·4. $C_{19}H_{25}O_4N_3S,HCl$ requires C, 53·3; H, 6·1; N, 9·6%). The *picrate* separated from aqueous alcohol in hexagonal yellow tablets, m. p. 156—157° (Found, after drying at 116° in a vacuum : C, 48·0; H, 4·5; S, 5·0. $C_{19}H_{25}O_4N_3S,C_6H_3O_7N_3$ requires C, 48·4; H, 4·5; S, 5·2%). The alkylation was later more conveniently carried out by refluxing a mixture of the components in ethanolic sodium ethoxide for 6 hours, but with some diminution in yield.

3-*Nitro*-β-*diethylaminoethylaniline.*—The foregoing hydrochloride (6·0 g.) was dissolved in sulphuric acid (55 c.c. of 95%), and after standing overnight, the solution was poured into ice-water and basified. The liberated *nitroamine* was collected in ether and on distillation obtained as a yellow-red oil (2·5 g., 75%), b. p. 125—130° (bath temp.)/0·03 mm. (Found : C, 61·1; H, 8·0. $C_{12}H_{19}O_2N_3$ requires C, 60·7; H, 8·0%), characterised by a *picrate*, which crystallised from aqueous alcohol in orange prisms, m. p. 151—152° (Found : C, 46·5 : H, 4·8. $C_{12}H_{19}O_2N_3,C_6H_3O_7N_3$ requires C, 46·4; H, 4·7%).

A specimen of the nitroamine (1·5 g.) was catalytically reduced in methanol (30 c.c.), and combined with violuric acid (2 g.) dissolved in water (10 c.c.) by heating on a steam-bath for 50 minutes. On cooling, a red-brown solid (1·6 g.), m. p. 290° (decomp.), was obtained, which dissolved in aqueous ethanol to a yellow solution with green fluorescence. It crystallised from water as a brick-red powder with a green lustre, m. p. 300° (decomp.), and consisted of a *violurate*, possibly of 7-amino-9-β-diethylaminoethyl*iso*alloxazine and of the isomeric alloxazine, but its constitution was not definitely ascertained (Found, after drying at 120° in a vacuum : C, 49·6, 49·3; H, 5·2, 5·2; N, 25·6. $C_{16}H_{20}O_2N_6,C_4H_3O_4N_3$ requires C, 49·5; H, 4·7; N, 26·0%).

6 : 7-*Dimethoxyalloxazine.*—(i) 4-Nitroveratrole (2 g.) was catalytically reduced in dioxan (15 c.c.), and the amine obtained by evaporation to dryness was dissolved in acetic acid (15 c.c.). Violuric acid (1·72 g.) was then added, and the mixture heated under reflux for 10 hours. The dark maroon product (0·34 g.) was collected on cooling, and purified by repeatedly dissolving it in 1% aqueous sodium hydroxide and reprecipitating it with acid. The light yellow-brown 6 : 7-*dimethoxyalloxazine*, m. p. 333—335° (decomp., with darkening >300°), dissolved in alkali to a yellow solution with a brilliant green fluorescence (Found, after drying at 150° in a vacuum : C, 52·5; H, 4·1. $C_{12}H_{10}O_4N_4$ requires C, 52·6; H, 3·6%). The pure alloxazine gave an intense red solution in concentrated sulphuric acid which underwent slight charring on heating.

(ii) 4 : 5-Dinitroveratrole (1·1 g.) in methanol (20 c.c.) was hydrogenated over Raney nickel, and the filtered solution heated with concentrated hydrochloric acid and alloxan monohydrate (0·9 g.) in water (10 c.c.). The yellow precipitate was purified as before, the alkaline solution being kept hot during acidification to minimise gel formation. The resulting alloxazine, m. p. >345° (decomp., with previous darkening), was a *sesquihydrate* (Found : C, 48·2; H, 4·2; N, 18·4. $C_{12}H_{10}O_4N_4,1\frac{1}{2}H_2O$ requires C, 47·8; H, 4·3; N, 18·6%) which lost water slowly at 150° in a vacuum (Found : C, 51·7; H, 4·0%). The intense red solution in sulphuric acid remained clear on heating.

The ultra-violet spectra of the two specimens in N/10-sodium hydroxide show the following characteristics :

Specimen (i).				Specimen (ii).			
λ max.	ε max.	λ max.	ε max.	λ max.	ε max.	λ max.	ε max.
2300	26,900	4050	8700	2200	20,600	4150	10,400
2600	26,900	λ min.	ε min.	2600	26,400	λ min.	ε min.
(3500	6,900) *	3000	2500	3500	7,150	3000	2,090

* The value of ε at 3500 A. : no extinction maximum was apparent in the curve at this wave-length.

5-Chloro-2-nitro-(β-diethylaminoethyl)aniline.—2 : 4-Dichloronitrobenzene (11·5 g.), β-diethylaminoethylamine (7 g.), and anhydrous sodium acetate were heated at 100° rising to 150° during 5 hours. Water (35 c.c.) and concentrated hydrochloric acid (18 c.c.) were then added, and the resulting solid collected and washed with ether. *5-Chloro-2-nitro-(β-diethylaminoethyl)aniline hydrochloride* (11·7 g., 63%) was thus obtained, which on crystallisation from aqueous ethanol formed yellow prisms, m. p. 208—209° (Found : C, 46·9; H, 6·1; Cl, 22·8. $C_{12}H_{18}O_2N_3Cl,HCl$ requires C, 46·8; H, 6·2; Cl, 23·1%). A solution in water gave with alkali the *chloronitroamine*, fine yellow needles from ethanol, m. p. 77—78° (Found : C, 53·0; H, 6·8; Cl, 13·0. $C_{12}H_{18}O_2N_3Cl$ requires C, 53·0; H, 6·6; Cl, 13·1%). The *picrate* crystallised from aqueous ethanol in long yellow prisms, m. p. 185—186° (Found : C, 43·6; H, 4·5; Cl, 7·1. $C_{12}H_{18}O_2N_3Cl,C_6H_3O_7N_3$ requires C, 43·2; H, 4·2; Cl, 7·1%).

7-Chloro-9-β-diethylaminoethylisoalloxazine.—The above nitro-amine (3·1 g., 1 mol.) was catalytically reduced in methanol (40 c.c.), and the colourless solution mixed with concentrated hydrochloric acid (3·5 c.c., 3 mols.) and alloxan monohydrate (2 g., 1·1 mols.) in hot water was heated to boiling for ½ hour. Evaporation to dryness and treatment of the residue with alcohol–acetone gave the iso*alloxazine hydrochloride* as a brown solid (1·8 g., 41%), which after repeated crystallisation from aqueous ethanol formed pale yellow prisms, m. p. 288—289° (decomp.) (Found : C, 49·0; H, 5·1; N, 17·7; Cl, 18·6. $C_{16}H_{18}O_3N_5Cl,HCl,\frac{1}{2}H_2O$ requires C, 48·8; H, 5·1; N, 17·8; Cl, 18·1%). The *picrate* crystallised from ethanol–water in pale yellow needles, m. p. 232° (decomp.) (Found : C, 45·8; H, 3·9; N, 19·0. $C_{16}H_{18}O_2N_5Cl,C_6H_3O_7N_3$ requires C, 45·8; H, 3·6; N, 19·4%).

5-Chloro-2-nitro-(γ-diethylaminopropyl)aniline.—A mixture of diethylaminopropylamine (15·6 g.), 2 : 4-dichloronitrobenzene (23 g.), and anhydrous sodium acetate was heated from 100° rising to 150° during 4 hours, and the 5-chloro-2-nitro-(γ-diethylaminopropyl)aniline isolated as *hydrochloride* by the addition of concentrated hydrochloric acid (40 c.c.) and water (80 c.c.). The product (37 g., 96%), m. p. 210°, crystallised from aqueous ethanol in yellow-orange needles, m. p. 224° (Found : C, 48·6; H, 6·5; N, 12·7; Cl, 22·9. $C_{13}H_{20}O_2N_3Cl,HCl$ requires C, 48·4; H, 6·5; N, 13·0; Cl, 22·0%). The *amine* was a pale yellow oil, b. p. 155—160°/0·3 mm. (Found : C, 54·6; H, 7·3; N, 14·9. $C_{13}H_{20}O_2N_3Cl$ requires C, 54·6; H, 7·0; N, 14·7%), having a *picrate* which crystallised from aqueous ethanol in yellow prisms, m. p. 169—170° (Found : C, 44·5; H, 4·7; N, 16·2. $C_{13}H_{20}O_2N_3Cl,C_6H_3O_7N_3$ requires C, 44·4; H, 4·5; N, 16·3%).

*7-Chloro-9-(γ-diethylaminopropyl)*iso*alloxazine.*—A solution of the amine prepared by catalytic reduction of the foregoing nitro-compound (3·2 g.) in methanol (40 c.c.) gave on being heated to boiling with hydrochloric acid (3·4 c.c.) and alloxan monohydrate (2 g.) in water for ½ hour the iso*alloxazine hydrochloride.* This was isolated by evaporation to dryness and addition of ethanol–acetone as a brown powder (3·1 g., 70%), which on crystallisation from aqueous alcohol gave scintillating microscopic yellow-brown plates, m. p. 291—292° (decomp.) (Found, after drying at 120° in a vacuum : C, 51·1; H, 5·4; N, 17·4; Cl, 17·4. $C_{17}H_{26}O_2N_5Cl,HCl$ requires C, 51·2; H, 5·3; N, 17·6; Cl, 17·8%). The *picrate*, minute green-yellow prisms from ethanol–water, had m. p. 258° (decomp.) (rapid heating) (Found : C, 46·9; H, 4·1; Cl, 6·2. $C_{17}H_{26}O_2N_5Cl,C_6H_3O_7N_3$ requires C, 46·7; H, 3·9; Cl, 6·0%).

The 7-chloro*iso*alloxazines in 0·1% aqueous solution were inactive against *B. coli*, but inhibited the growth of diluted (1/1000) *Staph. aureus* broth culture. Similar results were obtained with the *iso*alloxazine (VI; R = $[CH_2]_2{\cdot}NEt_2$) as hydrochloride, but saturated aqueous solutions of the sparingly soluble compounds (VI; R = Me), (VIII), and (IX) showed no bacteriostatic properties for either organism. We are indebted to Dr. E. P. Abraham, Sir William Dunn School of Pathology, Oxford, for these tests.

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DYSON PERRINS LABORATORY, OXFORD. [*Received, January 12th*, 1948.]

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390. *The Thermodynamic Functions of the Vinyl Halides.*

By R. E. RICHARDS.

The thermodynamic functions, namely, entropy, free-energy function, heat-content function, and heat capacity, have been calculated for the vapours of vinyl chloride, bromide, and iodide, over the temperature range 291—1500° K.

SINCE there appear to be no accurate measurements of the thermodynamic functions of the vinyl halides in the literature, and in view of the importance of these substances, it was thought that the calculation of these quantities might be useful. The calculations have been made for vinyl chloride, bromide, and iodide over a wide range of temperatures. Similar calculations for vinyl chloride have been carried out by Godnev and Filatova [*Compt. rend.* (*Doklady*) *Acad. Sci. U.R.S.S.*, **1946**, **52**, 43] at a few temperatures.

The following calculations have been made using the fundamental constants given by Birge (*Rev. Mod. Physics*, **1941**, **13**, 233; *J.*, 1946, 219). The translational–rotational entropy at one atmosphere is then given by the equation :

$$S°_{t.r.} = 2{\cdot}2870\ (8 \log T + 3 \log M + \log ABC - 2 \log \sigma) - 9{\cdot}2069 \text{ e.u.}$$

The logarithms are to the base 10, T is the absolute temperature, M is the molecular weight, A, B, and C are the principal moments of inertia of the molecule in units $\times 10^{-40}$ g.-cm.^{2}, and σ is the symmetry number. The values of the entropy are, of course, the "virtual entropy" and do not include nuclear-spin contributions. The molecular dimensions and frequencies used and the results of the calculations are tabulated below. The moments of inertia were calculated by the method of Hirschfelder (*J. Chem. Physics*, 1940, **8**, 431) and inserted into the expression for $S°_{t.r.}$ together with the symmetry number, $\sigma = 1$, to give the results of the last three tables. In order to find the error introduced by the uncertainty in the molecular dimensions, the products of the moments of inertia were calculated for the most different possible dimensions, and the new values of $S°_{t.r.}$ computed. Errors in $S°_{t.r.}$ of the order of 0·1 e.u. can be obtained, so that, although the values for the entropies have been given to the second decimal place, it must be remembered that this could be subject to a maximum possible error of the order of 0·1 e.u. In the last three tables the various units are cals., °c., moles, except for $(H° - E°_0)$ which is in kcal./mole.

The vibrational contributions to these quantities are summed with the aid of the tables compiled by E. B. Wilson, junr., and corrected to the basis of new constants (see Taylor and Glasstone, " A Treatise on Physical Chemistry," Vol. 1), the vibrations being assumed harmonic. The errors involved in this assumption and in neglecting the existence of isotopic molecules are certainly not greater than other inaccuracies involved.

Molecular dimensions used.

	Bond lengths, A.*			$I \times 10^{40}$, g.-cm.^{2}.			
Compound.	C–H.	C=C.	C–Hal.	*A*.	*B*.	*C*.	ν, cm.$^{-1}$.†
C_2H_3Cl	1·08	1·38	1·69 ± 0·02	15·7	135·7	151·4	395, 622, 724, 895, 940, 1030, 1280, 1370, 1610, 3030, 3080, 3130
C_2H_3Br	1·08	1·34	1·86 ± 0·04	16·0	195·0	210	345, 497, 615, 902, 940, 1008, 1262, 1377, 1605, 3014, 3076, 3100
C_2H_3I	1·09	1·34	2·03 ± 0·04	17	240	257	309, 435, 535, 909, 946, 990, 1229, 1376, 1593, 3000, 3060, 3110

* C_2H_3Cl : Brockway, *J. Chem. Physics*, 1936, **8**, 231. C_2H_3Br and C_2H_3I : Hugill, Coop, and Sutton, *Trans. Faraday Soc.*, 1938, **34**, 1518. All angles are assumed to be 120°, except in vinyl iodide for which the HCH angle is 120° and the HCI angle is 122°.

† C_2H_3Cl and C_2H_3Br : Thompson and Torkington, *Proc. Roy. Soc.*, 1945, *A*, **184**, 21. C_2H_3I : *idem*, *J.*, 1944, 303.

Temp.,	Entropy.			$-(G° - E°_0)/T$.		$\frac{(H° - E°_0)}{T}$,		$(H° - E°_0)$,	
° K.	$S°_{t.r.}$.	$S_{vib.}$.	$S°_{total}$.	Vib.	Total.	Vib.	Total.	$C_{vib.}$.	$C°_p$.
				Vinyl chloride.					
291·16	60·80	1·961	62·76	0·516	53·36	1·444	2·734	4·676	12·622
298·16	60·98	2·076	63·06	0·552	53·59	1·524	2·824	4·879	12·824
300	61·03	2·111	63·14	0·563	53·64	1·548	2·848	4·936	12·882
350	62·26	2·972	65·23	0·843	55·16	2·128	3·526	6·314	14·260
400	63·32	3·903	67·22	1·167	56·54	2·736	4·273	7·611	15·557
450	64·25	4·867	69·12	1·524	57·83	3·343	5·080	8·773	16·719
500	65·09	5·848	70·94	1·907	59·05	3·940	5·943	9·841	17·787
550	65·85	6·831	72·68	2·311	60·21	4·520	6·856	10·791	18·737
600	66·54	7·810	74·35	2·728	61·32	5·082	7·817	11·658	19·604
650	67·18	8·770	75·95	3·155	62·39	5·615	8·815	12·432	20·378
700	67·77	9·719	77·48	3·591	63·41	6·128	9·852	13·143	21·089
750	68·31	10·649	78·96	4·031	64·40	6·619	10·923	13·797	21·743
800	68·83	11·560	80·39	4·473	65·35	7·087	12·026	14·401	22·347
850	69·31	12·445	81·75	4·914	66·28	7·532	13·156	14·955	22·901
900	69·76	13·321	83·08	5·360	67·18	7·961	14·316	15·542	23·488
1000	70·60	15·003	85·60	6·244	68·90	8·758	16·704	16·398	24·344
1200	72·04	18·129	90·18	7·966	72·07	10·164	21·731	17·897	25·843
1500	73·82	22·302	96·12	10·422	76·30	11·879	29·738	19·491	27·437

Temp., ° K.	Entropy. $S°_{tr.}$	$S_{vib.}$	$S°_{total}$	$-(G° - E°_0)/T$. Vib.	Total.	$\frac{(H° - E°_0)}{T}$, Vib.	Total.	$(H° - E°_0)$, $C_{vib.}$	$C°_p$.
				Vinyl bromide.					
291·16	63·11	2·560	65·67	0·738	55·90	1·823	2·844	5·301	13·247
298·16	63·29	2·689	65·98	0·782	56·13	1·907	2·938	5·492	13·437
300	63·34	2·723	66·06	0·794	56·19	1·929	2·962	5·541	13·487
350	64·57	3·677	68·24	1·137	57·76	2·540	3·670	6·862	14·808
400	65·63	4·675	70·30	1·516	59·20	3·159	4·442	8·087	16·033
450	66·56	5·693	72·26	1·923	60·54	3·769	5·272	9·204	17·150
500	67·40	6·715	74·12	2·351	61·81	4·364	6·155	10·211	18·157
550	68·16	7·732	75·89	2·795	63·01	4·937	7·085	11·119	19·065
600	68·85	8·736	77·58	3·248	64·15	5·488	8·060	11·942	19·888
650	69·49	9·720	79·21	3·707	65·25	6·013	9·073	12·691	20·637
700	70·07	10·685	80·76	4·171	66·30	6·514	10·122	13·376	21·322
750	70·62	11·631	82·25	4·637	67·32	6·994	11·205	14·008	21·954
800	71·14	12·556	83·69	5·105	68·29	7·451	12·318	14·592	22·538
850	71·62	13·453	85·07	5·567	69·24	7·886	13·457	15·133	23·079
900	72·07	14·341	86·41	6·035	70·16	8·306	14·626	15·636	23·582
950	72·50	15·199	87·70	6·495	71·05	8·705	15·818	16·105	24·051
1000	72·91	16·031	88·94	6·948	71·91	9·084	17·029	16·538	24·484
1200	74·36	19·183	93·54	8·728	75·14	10·455	22·081	18·007	25·953
1500	76·13	23·379	99·51	11·247	79·43	12·132	30·117	19·573	27·518
				Vinyl iodide.					
291·16	64·65	3·063	67·71	0·943	57·65	2·120	2·931	5·714	13·659
298·16	64·84	3·202	68·04	0·995	57·89	2·207	3·027	5·896	13·842
300	64·89	3·237	68·13	1·009	57·95	2·229	3·052	5·944	13·890
350	66·11	4·250	70·36	1·398	59·57	2·852	3·779	7·218	15·164
400	67·17	5·295	72·47	1·821	61·05	3·474	4·568	8·401	16·347
450	68·11	6·343	74·45	2·263	62·43	4·080	5·412	9·479	17·424
500	68·95	7·392	76·34	2·724	63·72	4·668	6·307	10·450	18·396
550	69·74	8·433	78·17	3·196	64·99	5·237	7·251	11·338	19·284
600	70·40	9·454	79·85	3·676	66·13	5·779	8·235	12·138	20·084
650	71·03	10·459	81·49	4·161	67·25	6·298	9·258	12·868	20·814
700	71·62	11·439	83·06	4·647	68·32	6·792	10·317	13·537	21·483
750	72·17	12·390	84·56	5·129	69·35	7·261	11·406	14·154	22·099
800	72·68	13·324	86·01	5·613	70·35	7·711	12·525	14·726	22·672
850	73·16	14·299	87·39	6·091	71·31	8·138	13·672	15·255	23·201
900	73·62	15·122	88·74	6·572	72·24	8·550	14·846	15·750	23·696
950	74·05	15·982	90·03	7·043	73·14	8·940	16·041	16·207	24·153
1000	74·45	16·825	91·28	7·512	74·02	9·314	17·259	16·636	24·582
1200	75·90	19·994	95·90	9·333	77·29	10·661	22·328	18·080	26·026
1500	77·68	24·201	101·88	11·892	81·62	12·309	30·382	19·625	27·571

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LINCOLN COLLEGE, OXFORD. [*Received, January 13th*, 1948.]

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391. *Ethylidene Derivatives of Sorbitol.*

By E. J. BOURNE and L. F. WIGGINS.

Two substances, both claimed to be triethylidene D-sorbitol, have previously been reported by Appel (*J.*, 1935, 425) and by Sullivan (*J. Amer. Chem. Soc.*, 1945, **67**, 837). That of Appel is now shown to be triethylidene D-mannitol, whilst the true triethylidene D-sorbitol is the compound reported by Sullivan. A monoethylidene hexitol, isolated from crude triethylidene D-sorbitol syrup by hydrolysis, is shown to be a true sorbitol derivative and is in fact 2 : 4-ethylidene D-sorbitol. Confirmation is obtained of the structures of 1 : 3-2 : 4-diethylidene D-sorbitol and of 1 : 3-2 : 4-5 : 6-triethylidene D-sorbitol.

THE first systematic study of the ethylidene derivatives of sorbitol was reported by Appel (*loc. cit.*) who, after treating D-sorbitol with paraldehyde and hydrochloric acid, isolated triethylidene D-sorbitol as a syrup, and thence by hydrolysis diethylidene D-sorbitol. It was claimed that a small proportion of the triethylidene compound could be obtained crystalline, m. p. 174—176°, but that crystallisation was wasteful and unnecessary if the syrup was subsequently to be hydrolysed to the diethylidene derivative. More recently Sullivan (*loc. cit.*) prepared triethylidene D-sorbitol, having m. p. 96—97°, in 18% yield; he pointed out that this substance was different from that of Appel and considered that the two substances were possibly *cis-trans* or other isomers. In order to elucidate this interesting problem we have prepared from

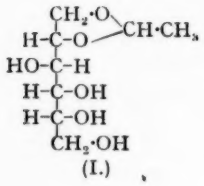
D-sorbitol by Appel's method " triethylidene sorbitol syrup " and have isolated from it both of the " triethylidene sorbitols " mentioned above. Crystallisation of the syrup from alcohol or water very readily gave a small yield (*ca.* 7%) of Appel's derivative, whilst Sullivan's compound could be isolated only after the residual syrup had been fractionally distilled. Even then this lower-melting isomer was difficult to crystallise.

It was noticed that the melting point of Appel's " triethylidene D-sorbitol " agreed closely with that reported by Meunier (*Compt. rend.*, 1889, **108**, 408) for triethylidene D-mannitol, which has now been prepared in good yield from D-mannitol. The melting points and specific rotations of the two compounds have been found to be identical and no depression of m.p. was observed on admixture. In addition, Appel's " triethylidene D-sorbitol " has been converted by hydrolysis and subsequent acetylation into crystalline D-mannitol hexa-acetate, isolated in 81% yield. Clearly, the " triethylidene D-sorbitol " reported by Appel is actually triethylidene D-mannitol, arising probably from mannitol present as an impurity in the commercial sorbitol.

Therefore it seemed probable that the isomeric triethylidene hexitol reported by Sullivan was a true sorbitol derivative, but no additional evidence could be found to support this contention since Sullivan, like Appel, conducted his subsequent experiments on the crude syrup. However, we have now prepared the true triethylidene D-sorbitol of Sullivan from diethylidene D-sorbitol, which, as is shown below, is amply proved to be a sorbitol derivative. Furthermore, this triacetal was converted by hydrolysis and subsequent acetylation into crystalline D-sorbitol hexa-acetate, which was recovered in 70% of the theoretical yield.

The structure of diethylidene D-sorbitol has been examined by several workers, all of whom have employed Appel's (*loc. cit.*) original method of preparation, namely, hydrolysis of the syrupy " triethylidene D-sorbitol " with aqueous acetic acid. The presence of two free hydroxyl groups in this product has been demonstrated by the isolation of a ditoluene-*p*-sulphonate (Wiggins, *J.*, 1946, 388; Sullivan, *loc. cit.*), a dibenzoate (Sullivan, *loc. cit.*), a dimethyl ether (Bourne and Wiggins, *J.*, 1944, 517), and a *diacetate*. Since one molecule of diethylidene D-sorbitol utilizes one atom of oxygen when oxidized with lead tetra-acetate in acetic acid solution (Bourne and Wiggins, *loc. cit.*), the two free hydroxyl groups are present as a glycol grouping, which is ruptured in this process to give a diethylidene derivative of L-xylose (Appel, *loc. cit.*). Moreover, Vargha and Puskas (*Ber.*, 1943, **76**, 859) effected the conversion of diethylidene D-sorbitol into D-sorbitol hexa-acetate. These facts clearly prove that the diethylidene compound is truly a derivative of D-sorbitol in which the hydroxyl groups on C_5 and C_6 are not involved in acetal linkages.

Only one communication (Gätzi and Reichstein, *Helv. Chim. Acta*, 1938, **21**, 86) throws any light on the finer structure of diethylidene D-sorbitol. These authors oxidised it with potassium permanganate in slightly alkaline solution and obtained diethylidene L-xylonic acid and monoethylidene L-threonic acid. The latter substance was shown to have its ethylidene residues attached to C_2 and C_4 of the threonic acid molecule, from which fact Gätzi and Reichstein deduced that the acetal groupings in diethylidene sorbitol were in the 1 : 3- and 2 : 4-positions. We have now confirmed this deduction by a different and more certain method.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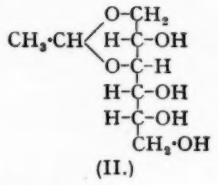
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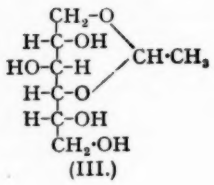
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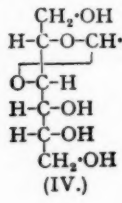
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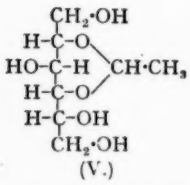
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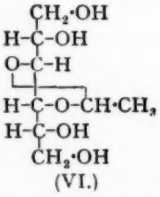
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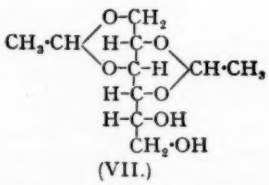
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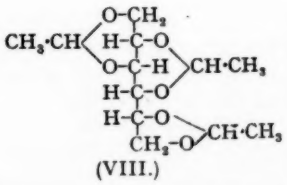
(VIII.)

Syrupy " triethylidene D-sorbitol " was hydrolysed with 50% aqueous acetic acid to Appel's diethylidene D-sorbitol, m. p. 212—213°. The addition of ether to the alcoholic mother-liquors from this crystallisation gave a ***monoethylidene hexitol***, which was also prepared by hydrolysis of

the crystalline diethylidene D-sorbitol itself and was thus shown to be a true derivative D-sorbitol. This conclusion was supported by the isolation in good yield of D-sorbitol hexa-acetate from the monoacetal by hydrolysis and subsequent acetylation. Direct acetylation of the monoethylidene D-sorbitol in pyridine solution gave the characteristic *tetra-acetate*.

Since the monoethylidene D-sorbitol was derived from diethylidene D-sorbitol, in which the hydroxyl groups on C_5 and C_6 are not engaged in acetal formation, it can have one of the structures (I)—(VI). However, when treated with lead tetra-acetate in acetic acid solution it utilized only one atom of oxygen per molecule, a fact which eliminated all these structures except (V). Therefore monoethylidene D-sorbitol is the 2 : 4-derivative and it follows that diethylidene D-sorbitol (VII) has 1 : 3- and 2 : 4-acetal groupings, whilst in triethylidene D-sorbitol (VIII) the acetaldehyde residues may be allocated to the 1 : 3-, 2 : 4-, and 5 : 6-positions.

Experimental.

Ethylidenation of Sorbitol.—When commercial D-sorbitol was shaken with paraldehyde and 40% hydrochloric acid according to Appel's method (*loc. cit.*), the so-called "triethylidene sorbitol syrup" was obtained in 51% yield. A variation of this procedure in which 48% hydrobromic acid was employed in the following way gave somewhat higher yields of condensation products. Sorbitol (50 g.) was shaken overnight with paraldehyde (150 c.c.) and 48% hydrobromic acid (20 c.c.). Chloroform (200 c.c.) and water (50 c.c.) were then added, the mixture shaken, and the chloroform extract separated and washed with dilute sodium hydrogen carbonate and with water. After being dried ($MgSO_4$), the extract was evaporated to a syrup (45·4 g.). This was diluted with 50% aqueous alcohol (200 c.c.) and the mixture allowed to stand overnight. Feathery needles separated (3·1 g., 7% of the weight of crude syrup), m. p. 172—174°, $[\alpha]_D^{20°}$ − 72·7° in chloroform (*c*, 0·8). This was identical with triethylidene mannitol (see below). A m. p. of these crystals in admixture with authentic triethylidene mannitol showed no depression. Appel (*loc. cit.*) isolated crystals from the crude triethylidene sorbitol syrup and quoted m. p. 174—176° (no $[\alpha]_D$ given). This is clearly identical with the product described here, although Appel described it as triethylidene sorbitol. The mother-liquors, after the separation of the feathery needles of triethylidene mannitol, were concentrated to a syrup which distilled almost completely at 102—108°/0·15 mm. The distillate crystallised on cooling and, recrystallised from ether–ligroin, formed short feathery needles of triethylidene sorbitol (12·4 g.), m. p. 92—95, $[\alpha]_D^{20°}$ − 20·2° in water (*c*, 4·52). Sullivan (*loc. cit.*) obtained a triethylidene sorbitol (18% from sorbitol) in white needles, m. p. 96—97°, $[\alpha]_D^{22°}$ − 21·6 in water (*c*, 5) (Found : C, 55·6; H, 7·6. Calc. for $C_{12}H_{20}O_6$: C, 55·4; H, 7·7%).

Triethylidene Mannitol from Mannitol.—Mannitol (20 g.) was shaken overnight with paraldehyde (75 c.c.) and 48% hydrobromic acid (10 c.c.). A crystalline precipitate separated. Chloroform was added until this dissolved. The solution was then washed with water, sodium hydrogen carbonate, and again with water. The extract was dried ($MgSO_4$), filtered, and evaporated to dryness. The residue (26·3 g.) completely crystallised, and when recrystallised from alcohol, the triethylidene mannitol formed feathery needles; yield 19·5 g., m. p. 172°, $[\alpha]_D^{20°}$ − 72·3° in chloroform (*c*, 0·8) (Found : C, 55·7; H, 8·0. Calc. for $C_{12}H_{20}O_6$: C, 55·4; H, 7·7%). Meunier (*loc. cit.*) prepared triethylidene mannitol by shaking mannitol with paraldehyde and sulphuric acid and described it as forming silky needles of m. p. 174° (rapid heating).

Mannitol Hexa-acetate from Triethylidene Mannitol.—Triethylidene mannitol (0·535 g.), which had been isolated from "triethylidene sorbitol syrup", was hydrolysed with N-hydrochloric acid (3 c.c.) at 100° for 2 hours. The solvent was removed under reduced pressure, and the syrup dried in a vacuum. Thereafter it was boiled for 40 minutes with acetic anhydride (6 c.c.) and fused sodium acetate (1·5 g.). When cold, the mixture was stirred into ice–water, and the ester extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated. The product (0·72 g.), recrystallised from aqueous alcohol, had m. p. 124·5—125·5°, alone or in admixture with authentic mannitol hexa-acetate. The m. p. was depressed in admixture with sorbitol hexa-acetate.

D-*Sorbitol Hexa-acetate from* 1 : 3-2 : 4-5 : 6-*Triethylidene* D-*Sorbitol.*—Triethylidene sorbitol (0·5 g.) was boiled for 2 hours with 5N-hydrochloric acid (25 c.c.). The solution was evaporated to dryness under reduced pressure, and the residue acetylated by boiling with acetic anhydride (15 c.c.) and fused sodium acetate (1 g.) for 20 mins. Thereafter the mixture was cooled and poured into ice–water, neutralized with sodium hydrogen carbonate and exhaustively extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to dryness. The residue, recrystallised from alcohol in prisms, had m. p. 100—101° alone or in admixture with an authentic specimen of hexa-acetyl sorbitol; yield 0·58 g., 70%.

Hydrolysis of "Triethylidene Sorbitol Syrup."—"Triethylidene D-sorbitol syrup" (108 g.) was hydrolysed with hot aqueous acetic acid according to Appel (*loc. cit.*). The solvent was removed under reduced pressure at 70°, leaving a syrup which was then stirred with alcohol (20 c.c.) and ether (200 c.c.). A white solid (28·1 g.) was precipitated; m. p. 190°. The mother-liquors were evaporated to a syrup, from which white needles of triethylidene D-mannitol (2 g.), m. p. 171°, separated on the addition of water (180 c.c.). The solid (m. p. 190°) was rapidly washed with a small volume of chloroform to remove any triethylidene derivative and twice recrystallised from the minimum volume of ethyl alcohol. The product was 1 : 3-2 : 4-diethylidene D-sorbitol (14·5 g.), m. p. 212—213°, $[\alpha]_D^{15°}$ − 10·9° in water (*c*, 5·5). Appel (*loc. cit.*) recorded m. p. 212—214°, $[\alpha]_D^{17°}$ − 11·1° in water (*c*, 2·3) for this compound.

The addition of excess of ether to the alcoholic mother-liquors gave a precipitate which, after being twice recrystallised from alcohol–ether, formed white needles (0·73 g.), $[\alpha]_D^{21°}$ − 4·6° in water (*c*, 2·2), m. p. 146°, depressed in admixture with 1 : 3-2 : 4-diethylidene D-sorbitol or triethylidene D-mannitol (Found : C, 46·4; H, 7·8. $C_8H_{16}O_6$ requires C, 46·1; H, 7·8%). This compound was 2 : 4-*ethylidene* D-*sorbitol*, and was prepared in larger quantity by the same method for further examination.

Acetylation of 1 : 3-2 : 4-*Diethylidene* D-*Sorbitol.*—Diethylidene sorbitol (0·252 g.) was dissolved in dry pyridine (2·5 c.c.), and acetic anhydride (0·30 c.c.) added. After being kept at room temperature for 24 hours, the mixture was poured into ice–water (30 c.c.). The precipitated 5 : 6-*diacetyl* 1 : 3-2 : 4-*diethylidene* D-*sorbitol*, recrystallised from aqueous alcohol, showed m. p. 153—154° and $[\alpha]_D^{23°}$ + 2·8° in chloroform (*c*, 1·1); yield 0·131 g. (Found: C, 52·9; H, 6·9. $C_{14}H_{22}O_8$ requires C, 52·8; H, 7·0%).

1 : 3-2 : 4-5 : 6-*Triethylidene* D-*Sorbitol from* 1 : 3-2 : 4-*Diethylidene* D-*Sorbitol.*—1 : 3-2 : 4-Diethylidene D-sorbitol (1·93 g.) was heated under reflux with chloroform (25 c.c.), paraldehyde (10 c.c.), and concentrated hydrochloric acid (5 c.c.) for 5 minutes and then kept at room temperature for 24 hours. The product was extracted with chloroform (100 c.c.). The extract was washed with water (20 c.c.), dried ($MgSO_4$), and evaporated to a syrup which crystallised on cooling. Recrystallised several times from light petroleum (b. p. 60—80°) in white needles, 1 : 3-2 : 4-5 : 6-triethylidene D-sorbitol showed m. p. 94—95°

2 : 4-*Monoethylidene* D-*Sorbitol from* 1 : 3-2 : 4-*Diethylidene* D-*Sorbitol.*—Diethylidene sorbitol (2·08 g.) was heated under reflux on a boiling water-bath with 50% acetic acid (by vol.) (20 c.c.) for 2·5 hours. The solution was evaporated under reduced pressure at 40° to a viscous syrup, which was redissolved in chloroform (30 c.c.). The solution was passed under gravity through a column (1 cm. diameter by 37 cm.) of activated alumina which had already been saturated with chloroform. The column was then washed with the following solvents, the surface of the liquid always being maintained level with the top of the alumina: (*a*) Chloroform (25 c.c.); evaporation of the eluate revealed the presence of only a trace of brown syrup. (*b*) Chloroform–alcohol (1 : 1 by vol., 20 c.c.); the eluate was evaporated, leaving a white solid which, after crystallisation from alcohol, gave a product having m. p. 209—212° (slightly impure diethylidene sorbitol). (*c*) Chloroform–alcohol (1 : 1 by vol., 20 c.c.); the syrup isolated from the eluate by evaporation was twice recrystallised from acetone containing a few drops of alcohol, and the white needles obtained (0·061 g.) had m. p. 144—146·5°, not depressed in admixture with the 2 : 4-monoethylidene sorbitol obtained as above. (*d*) Alcohol (25 c.c.); treatment of the eluate as in (*c*) yielded 2 : 4-monoethylidene sorbitol (0·146 g.), m. p. 146—148°. (*e*) Alcohol (100 c.c.); this extracted a white solid (0·020 g.), m. p. 50—55°.

From the combined acetone mother-liquors of (*c*) and (*d*) a further amount (0·044 g.) of 2 : 4-monoethylidene sorbitol was isolated.

D-*Sorbitol Hexa-acetate from* 2 : 4-*Monoethylidene* D-*Sorbitol.*—2 : 4-Monoethylidene D-sorbitol (0·195 g.) was hydrolysed by heating at 100° for 1 hour with N-hydrochloric acid (2·5 c.c.). The solvent was removed, and the residue dried in a vacuum. It was acetylated by boiling for 45 minutes with fused sodium acetate (0·5 g.) and acetic anhydride (2·0 c.c.). The cold mixture was stirred with ice–water (25 c.c.). Recrystallisation of the precipitate from aqueous alcohol yielded a product (0·126 g.), m. p. 99·5—100·5°, alone or in admixture with authentic sorbitol hexa-acetate; in contrast, the m. p. was markedly depressed by admixture with mannitol hexa-acetate. A second crop (0·209 g.) of sorbitol hexa-acetate (m. p. 98—100·5°) was recovered from the aqueous filtrate by extraction with chloroform, evaporation, and recrystallisation from aqueous alcohol.

Acetylation of 2 : 4-*Monoethylidene* D-*Sorbitol.*—2 : 4-Monoethylidene D-sorbitol (0·070 g.) was dissolved in dry pyridine (1·5 c.c.), and acetic anhydride (0·30 c.c.) added. The mixture was kept at room temperature for 48 hours. Thereafter it was cooled, poured into ice-water (25 c.c.), and exhaustively extracted with chloroform. The extract was washed with dilute sulphuric acid, dilute sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and evaporated to a syrup, which crystallised on cooling. After being recrystallised twice from aqueous alcohol, *tetra-acetyl* 2 : 4-*monoethylidene* D-*sorbitol* was isolated in white needles (0·095 g.),m. p. 117—118° (Found: C, 51·4; H, 6·3; Ac, 46·7. $C_{16}H_{24}O_{10}$ requires C, 51·1; H, 6·4; Ac, 45·7%).

Oxidation of Di- and Mono-ethylidene Sorbitol and Triethylidene Mannitol with Lead Tetra-acetate.—The method of Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667) being used, the following values were calculated for the number of g.-atoms of oxygen taken up by 1 g.-mol. of the compound used. The same solution of lead tetra-acetate was employed in each case and 0·0005 mol. of each substance was used: (*a*) 1 : 3-2 : 4-Diethylidene D-sorbitol: 0·14 (8 mins.); 0·55 (60 mins.); 0·76 (120 mins.); 0·87 (180 mins.); 0·95 (290 mins.). (*b*) 2 : 4-Monoethylidene D-sorbitol: 0·14 (8 mins.); 0·54 (60 mins.); 0·76 (120 mins.); 0·87 (180 mins.); 0·95 (290 mins.). (*c*) Triethylidene D-mannitol: 0·00 (8—290 mins.).

The authors are indebted to Professor Sir Norman Haworth for his interest in this work, and to Miss Mary J. Nicholls and Dr. P. Harvey for practical assistance.

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392. *The Isolation of Uridine from Yeast Ribosenucleic Acid.*

By R. J. C. HARRIS and J. F. THOMAS.

An improved method has been found for the isolation of uridine from yeast ribosenucleic acid. It is now possible to separate and identify the two purine and two pyrimidine nucleosides from small samples of the nucleic acid.

THE chemical investigation of small amounts of pentosenucleic acids which may be derived from different plant and animal sources is difficult, and the identity of these acids has frequently been assumed on the evidence of unspecific colour reactions for the identification of the pentose or of qualitative tests for the nitrogenous bases. Where larger amounts are available, it is usually

possible to isolate the individual nucleotides or nucleosides for comparison with those obtained by similar methods from yeast ribosenucleic acid. Thus it has been established that adenylic, guanylic, cytidylic, and uridylic acids may be obtained from wheat-embryo nucleic (" triticonucleic ") acid (Calvery and Remsen, *J. Biol. Chem.*, 1927, **73**, 593) which are identical with those obtained from yeast. Similarly two purine and two pyrimidine nucleosides have been obtained from chick-embryo nucleic acid (Calvery, *ibid.*, 1928, **77**, 489), and more recently Schwerdt and Loring (*ibid.*, 1947, **167**, 593) were able to isolate very small quantities of diammonium uridylate, cytidylic acid, and brucine guanylate from tobacco-mosaic virus pentosenucleic acid.

As a preliminary to the study of the nucleic acids of normal and tumour tissue an investigation has been made of the preparation of the purine and pyrimidine nucleosides of yeast ribosenucleic acid.

Gulland and Hobday (*J.*, 1940, 746), using a modification of the Levene method of ammonia hydrolysis (Levene and Bass, " Nucleic Acids ", 1931, Reinhold Publishing Corp., p. 162; Levene and Jacobs, *Ber.*, 1909, **42**, 2471, 2476; 1910, **43**, 3154), prepared 6 g. of uridine from 100 g. of B.D.H. yeast nucleic acid and in this preparation all the cytidine present was deaminated to uridine.

Bredereck, Martini, and Richter (*Ber.*, 1941, **74**, 694) claimed to have obtained 2—3 g. of uridine and 4 g. of cytidine (no melting points or analytical data are given) from 100 g. of nucleic acid by either enzymatic or aqueous pyridine hydrolysis. Since both methods gave identical yields it is reasonable to assume that losses were due, not to incomplete hydrolysis, but to poor separative methods. Gulland and Smith (*J.*, 1947, 338) modified Bredereck's method and, incorporating the cytidine deamination procedure, obtained yields of 17·5—22·5 g. of uridine from 360 g. of nucleic acid. These authors were unable, after several attempts, to prepare cytidine by Bredereck's method.

Despite the large quantities of nucleic acid used, demonstration of all four nucleosides in the same hydrolysis sample has not readily been forthcoming.

In the method to be described, guanosine, adenosine, and uridine can be obtained in good yield from the pyridine hydrolysate of quite small (20 g.) quantities of yeast nucleic acid, and smaller quantities of cytidine (as cytidine sulphate) have been isolated at the same time. From the removal of adenosine to the crystallisation of uridine the Gulland–Bredereck procedure involves seventeen stages, whereas uridine and cytidine can now be separated in one operation.

The amino-group in cytidine has pK 4·22, and the nucleoside is adsorbed from aqueous solution by suitably-prepared cation-exchange resins. When a mixture of cytidine and uridine is percolated through a column of " Zeo-Karb 215 ", cytidine is retained by the resin and uridine alone appears in the effluent. Washing with water removes the uridine quantitatively, and the cytidine may subsequently be recovered by treatment of the resin with aqueous pyridine.

For convenience in handling the column a simple method of determining uridine and cytidine has been used. In aqueous solution both pyrimidine nucleosides react quantitatively at room temperature with free bromine with the formation of 5-bromouridine and 5-bromocytidine respectively. Free bromine is obtained by the normal bromide–bromate method, and reacts: Uridine + Br_2 = 5-bromouridine + HBr.

The operation is conducted in reagent bottles fitted with ground-glass stoppers, and the excess of bromine is determined iodometrically. Guanosine, adenosine, and free pentose (in this case, arabinose) do not interfere under the conditions of the determination. Uracil (and, presumably, cytosine) does interfere, and no selectivity is claimed for this method. It is useful, however, in the analysis of solutions of known composition where other methods of nucleoside determination are cumbersome.

This method of separating the pyrimidine ribosides is equally applicable to the separation of the pyrimidine deoxypentosides derived from deoxypentosenucleic acids, and an investigation of these acids has been started.

The successful recovery of pyrimidine ribosides from small quantities of yeast nucleic acid indicates that it will now be possible to obtain chemical data for the identification of the hydrolysis products of those nucleic acids which are not available on a centigramme or even decigramme scale.

Experimental.

Preparation of a Column of Cation-exchange Resin.—The exchange column consisted of a vertical glass tube 50 cm. in length and 3·5 cm. in diameter, having a side-arm 10 cm. from the top and fitted at the bottom with a sintered glass disc (to support the resin) and a tap. Enough " Zeo-Karb 215 " (The Permutit Co., Ltd.) to fill the column to a height of 27 cm. was soaked for 24 hours in sufficient

hydrochloric acid (2 parts acid, *d* 1·18, to 1 part water) to cover it. The column was then washed backwards with just sufficient head of distilled water to produce a gentle turbulence. The washing water flowed out through the side-arm. This method of washing serves the double purpose of grading the bed and effecting the removal of very fine debris which would otherwise clog the column. The resin in this condition actively removes cations from solution. It may be exhausted with sodium chloride solution (hydrochloric acid appearing in the effluent) and regenerated by treatment with 2N-hydrochloric acid. Usually an exchanger is ready for use after two or three exhaustion-regeneration cycles. After each regeneration the column is first back-washed with distilled water as described above and the washing completed by percolation in the normal direction until the effluent is free from chloride ion.

Preparation of Specimens of Guanosine, Adenosine, Cytidine, Uridine.—By the method of Bredereck *et al.* (*loc. cit.*) comparable yields were obtained of guanosine [colourless plates, m. p. 240° (sinters 235°), from water], and of adenosine (colourless needles, m. p. 228°, from water). Adenosine picrate, yellow plates, had m. p. 182°.

The pyrimidine nucleoside-containing residues were used to prepare uridine (in poor yield) by the method of Gulland and Hobday (*loc. cit.*). Uridine crystallised as colourless needles, m. p. 165—166°, from dilute alcohol; 5-bromouridine, needles, had m. p. 181—183°.

Cytidine was prepared by pyridine hydrolysis of cytidylic acid (Gulland and Smith—private communication). 6 G. of cytidylic acid gave 3 g. of cytidine as colourless needles, m. p. 230—233°, from dilute alcohol. Cytidine sulphate also crystallised in needles, m. p. 224—225° (decomp.), from dilute alcohol containing a drop of dilute sulphuric acid.

Levene records m. p. of 233° for cytidine sulphate, but the lower figure is accepted by Howard, Lythgoe, and Todd (*J.*, 1947, 1052) for the sulphate of synthetic cytidine.

Volumetric Determination of Uridine and Cytidine.—Hydrochloric acid (10 c.c.; N) and potassium bromide solution (5 c.c.; 10%) were added to the nucleoside solution (10 c.c.) (containing 1—10 mg.) or water (10 c.c.) (for determination of the blank) in a small reagent bottle fitted with a ground-glass stopper. The solution was titrated with 0·01N-potassium bromate until excess of bromine was present. It was usually an advantage to determine roughly the amount of bromate required and to use a 50% excess in further determinations. The same excess could then be used in the blank estimation. The bottle was then stoppered and allowed to stand at room temperature for 20 minutes. Potassium iodide solution (5 c.c.; 10%) was added, and the liberated iodine titrated immediately with 0·01N-sodium thiosulphate, using a starch indicator.

1 c.c. of 0·01N $KBrO_3$ = 1·216 mg. of uridine.

The accuracy of the determinations is indicated in the table.

Uridine present (mg.).	Cytidine present (mg.).	Uridine found (mg.).	Cytidine found (mg.).	Uridine present (mg.).	Cytidine present (mg.).	Uridine found (mg.).	Cytidine found (mg.).
0·984	—	0·984	—	4·920	—	4·860	—
1·968	—	1·930	—	—	1·999	—	1·960
3·836	—	3·750	—	—	3·998	—	3·995
4·920	—	4·840	—	—	4·998	—	4·970
4·920	—	5·020	—	0·492 +	5·050	5·650	
				2·461 +	2·525	5·090	

The last two results show the determination of total nucleoside in a mixture of cytidine and uridine. In comparable quantities adenosine and arabinose took up no bromine.

Behaviour of Individual Nucleosides on the Exchanger Column.—In these experiments a smaller column of resin was employed of length 14 cm. and diameter 1·7 cm. This had one-tenth the cation capacity of the larger column described above.

Adenosine. 50 C.c. of solution containing 250 mg. of adenosine were percolated through the column, which was then washed with an equal volume of water. The combined effluents were evaporated to dryness. No adenosine or solid material was present. The column was then stripped with 2% pyridine (100 c.c.), and the effluent concentrated under reduced pressure at 30—40°. Addition of a saturated solution of picric acid in water gave a quantitative yield of a picrate, as yellow platelets, m. p. 182° (undepressed by admixture with adenosine picrate). Elution of the column with 20% pyridine instead of 2%, however, produced considerable heat, the adenosine was hydrolysed *in situ*, and adenine picrate, m. p. 278—280° (decomp.), was recovered.

Cytidine. In similar experiments it was found that cytidine was retained completely by the resin and could be liberated with 2% pyridine.

Uridine. A solution of 250 mg. of uridine in 50 c.c. of water was percolated through the column in the usual way. The combined effluents contained (by volumetric determination, in which 10 c.c. of water washings of the column before use gave a negligible blank) 246 mg. of uridine thus: (*a*) 12 c.c. (= "dead space"), nil; (*b*) 50 c.c., 181 mg.; (*c*) 50 c.c., 65 mg.; (*d*) 50 c.c., nil.

Cytidine–uridine mixture. The solution contained 99·7 mg. of uridine and 37·0 mg. of cytidine in 100 c.c. 200 C.c. of initial effluent contained, by analysis, 95·5 mg. of uridine. The 2% pyridine effluent contained 26·0 mg. of cytidine.

The Separation of Uridine and Cytidine from the Pyridine Hydrolysate of Yeast Ribosenucleic Acid.—The hydrolysis of 20 g. of yeast nucleic acid (Pharmaco-Chemical Products Co.) with 50% pyridine and the separation of the guanosine and adenosine were carried out substantially by the method of Bredereck, Martini, and Richter (*loc. cit.*), and similar yields were obtained. The filtrate from the precipitation of the adenosine was concentrated under reduced pressure with repeated addition of water until all the alcohol had been removed. Residual purine nucleosides were hydrolysed with 2% sulphuric acid, and the liberated purines precipitated with hot silver sulphate solution. Excess of silver was removed as silver sulphide, and the solution was freed from SO_4^{--} quantitatively by addition of barium carbonate and diluted to 1 l. Percolation through the larger exchange column and washing with water gave 2 l. of effluent,

which, on concentration under reduced pressure, yielded 3·1 g. of brown crystalline material. Recrystallisation from dilute alcohol (charcoal) gave 2·4 g. of colourless needles, m. p. 165—166°, undepressed by admixture with uridine prepared by the Gulland–Bredereck procedure. $[\alpha]_D^{22^\circ} + 10{\cdot}0^\circ \pm 2^\circ$ (*c*, 1·6245 in water) (Found, in material dried at 80°/0·1 mm.: C, 43·8; H, 5·0. Calc. for $C_9H_{12}O_6N_2$: C, 44·2; H, 5·0%).

The column was then stripped in the usual way with 2% pyridine (1·6 l.), and washed with water (650 c.c.). The combined solutions were concentrated under reduced pressure to 10 c.c., 0·7 c.c. of concentrated sulphuric acid was added, and cytidine sulphate precipitated by addition of alcohol. Recrystallisation from dilute alcohol containing a drop of dilute sulphuric acid gave 150 mg. of colourless needles, m. p. 224—225° (decomp.) undepressed by admixture with cytidine sulphate prepared from cytidylic acid. $[\alpha]_D^{21^\circ} + 37{\cdot}0^\circ \pm 2^\circ$ (*c*, 1·498 in 1% aqueous sulphuric acid) [Found, in material dried at 110°/0·1 mm.: C, 37·3; H, 4·7. Calc. for $(C_9H_{13}O_5N_3)_2,H_2SO_4$: C, 37·0; H, 4·8%].

This low yield of cytidine is most probably due to destruction of the nucleoside by the acid treatment designed to hydrolyse the residual purine nucleosides.

In a further separation of a similarly-derived mixture, 1·95 g. of uridine and 140 mg. of cytidine sulphate were obtained. The amounts of uridine made available by this process are thus considerably in excess of those normally obtained by previous methods.

The thanks of the authors are due to Professor G. A. R. Kon, F.R.S., for his encouragement; to the University of London for the Laura de Saliceto studentship awarded to one of them (R. J. C. H.); and to the British Empire Cancer Campaign, the Jane Coffin Childs Memorial Fund for Medical Research, and the Anna Fuller Fund, for financial support.

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393. *Chemotherapeutic Agents of the Sulphone Type. Part V. 2 : 5-Disubstituted Derivatives of Pyridine.*

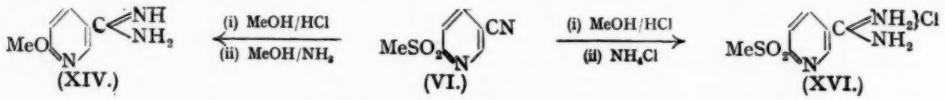
By H. S. FORREST and JAMES WALKER.

Replacement of the benzene ring in *p*-methylsulphonylbenzamidine hydrochloride, *p*-methylthiobenzamidine hydrochloride, and *p*-methylsulphonylaniline by a pyridine ring greatly reduced antibacterial activity in each case. Relatively marked antibacterial activity has been observed in some mercaptopyridines. A facile replacement of a methylsulphonyl substituent by a methoxy-group in the 2-position of the pyridine ring has been observed.

NUMEROUS reports have shown that the isosteric replacement of an aromatic ring in an essential metabolite affords a substance with antagonistic properties, and the wide generality of this biological discrimination has been borne out by studies on adenine, guanine, hypoxanthine, riboflavin, thiamin, nicotinic acid (and amide), phenylalanine, and *p*-aminobenzoic acid (for references, see Roblin, *Chem. Reviews*, 1947, **38**, 255; Woolley, *Physiol. Rev.*, 1947, **27**, 308). In the case of antibacterial agents, whether modelled on essential metabolites or otherwise, it is impossible to state in advance of experiment what will be the precise effect of similar replacement on biological activity. Comparative figures do not appear to be available for the activities of aminopyridinesulphonamides (*e.g.*, Naegeli *et al.*, *Helv. Chim. Acta*, 1938, **21**, 1746; Caldwell and Kornfeld, *J. Amer. Chem. Soc.*, 1942, **64**, 1695; Caldwell, Tyson, and Lauer, *ibid.*, 1944, **66**, 1479; B.P. 516,288) relative to the activities of the corresponding benzenoid analogues but the replacement of the benzene ring in sulphonamides by isosteric heterocyclic rings probably has a dystherapeutic effect generally (Tullar, quoted by Naegeli *et al.*, *loc. cit.*; Backer and de Jonge, *Rec. Trav. chim.*, 1943, **62**, 163). Among diamidines, the (bis)pyridine analogue of pentamidine has less than half the activity of the benzenoid compound (Gregory, Holt, and Slack, *J.*, 1947, 87). On the other hand, the antitubercular activities of 5-amino-2-alkoxypyridines and *p*-aminophenyl alkyl ethers are approximately equal for the same alkyl radical (C_4—C_6) (Feinstone *et al.*, *J. Pharmacol.*, 1947, **89**, 153). The work described in the present paper was undertaken, in part, to see if the outstanding antibacterial activity of some of the benzene derivatives studied in previous parts (*J.*, 1945, 630, 633) was shared by their pyridine analogues.

6-Chloronicotinamide (I) was dehydrated with phosphoryl chloride to give 2-chloro-5-cyanopyridine (II), which has been prepared by Rath (*Annalen*, 1931, **487**, 127) by a lengthier process, and the latter reacted smoothly with thiourea to give S-(*5-cyano-2-pyridyl*)*thiouronium chloride* (III). Decomposition of (III) with alkali afforded 5-cyano-2-mercaptopyridine (IV), which was obtained by Rath (*loc. cit.*) in much poorer yield from (II) and potassium hydrogen sulphide. Methylation of (IV) afforded *5-cyano-2-methylthiopyridine* (V), which yielded *5-cyano-2-methylsulphonylpyridine* (VI) on oxidation with potassium permanganate. Traces

of 6-*methylsulphonylnicotinamide* (VII) were formed during the oxidation and the possibility of postponing dehydration until the last stage in the preparation of (VI) suggested itself. As the amide group in (I) activates the chlorine atom less powerfully than the cyano-group does that in (II), reaction between (I) and thiourea was slower and less complete than the corresponding reaction of (II), but the resulting S-(5-*carbamyl*-2-*pyridyl*)*thiouronium chloride* (VIII) afforded easy access to 6-*mercaptonicotinamide* (IX), 6-*methylthionicotinamide* (X), (VII), and (VI). In the oxidations of thioethers with potassium permanganate described in this paper it was found that only $\frac{3}{6}$ of the oxygen usually available in acid solution appeared to be utilised and good yields of sulphones resulted on augmenting the amount of permanganate used on that basis. Oxidation of (X) with hydrogen peroxide only proceeded as far as 6-*methylsulphinylnicotinamide* (XI), the melting point of which, in contrast to the usual ascending series (thioether, sulphoxide, sulphone), was higher than that of (VII). Considerable difficulty was experienced in preparing amidines from (IV) and (V), owing to the ready precipitation of the starting materials as hydrochlorides at the outset with consequent recovery of substantial amounts of unchanged nitrile, and only moderate yields of 6-*mercaptonicotinamidine hydrochloride* (XII) and 6-*methylthionicotinamidine benzoate* (XIII) were obtained. Conversion of (VI) into the iminoether hydrochloride appeared to proceed more completely using methyl alcohol, and methyl-alcoholic ammonia, allowing of a higher concentration of ammonia, was used in the second stage of the Pinner process for amidine formation. Unexpectedly, however, the product proved to be 6-methoxynicotinamidine (XIV), which was characterised as the *benzoate* and

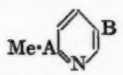


acetate, formed by displacement of the methylsulphonyl radical of (VI) by a methoxy-group, the identity of the salts being confirmed by comparison with authentic specimens. It was anticipated that displacement had taken place during imino-ether formation since nucleophilic displacement of potential anions occupying activated positions in heterocyclic compounds is catalysed by acids (Banks, *J. Amer. Chem. Soc.*, 1944, **66**, 1127; Tomisek and Christensen, *ibid.*, 1945, **67**, 2112; Walker, unpublished); similarly, the chlorine atom in 5-chloroacridine is fairly stable to hydrolysis (Graebe and Lagodzinski, *Annalen*, 1892, **276**, 48; Magidson and Grigorowski, *Ber.*, 1933, **66**, 866), but, when a formal positive charge rests on the nitrogen atom, hydrolysis takes place in aqueous solution with extreme readiness, as in the conversion of 5-chloro-*N*-methylacridinium chloride into *N*-methylacridone (Fischer and Demeler, *Ber.*, 1899, **32**, 1307). As a model, 5-*nitro*-2-*methylsulphonylpyridine* (XV), in which the activating forces would be comparable with those obtaining in (VI), was submitted to the conditions used for imino-ether formation and it was recovered unchanged. Treatment with methyl-alcoholic ammonia under the conditions used for the second stage of amidine formation, however, afforded 5-nitro-2-aminopyridine together with a small amount of 5-nitro-2-methoxypyridine, recalling the behaviour of 1-chloro-2 : 4-dinitrobenzene, to which (XV) bears some analogy, in reacting with alcoholic ammonia to give 2 : 4-dinitroaniline (Willgerodt, *Ber.*, 1876, **9**, 978) and with methyl-alcoholic potassium hydroxide to give 2 : 4-dinitroanisole (*idem*, *ibid.*, 1879, **12**, 763). It is noteworthy, too, that 1-chloro-2 : 4-dinitrobenzene reacts with aqueous-alcoholic sodium sulphite to give 2 : 4-dinitrobenzenesulphonic acid (D.R.-P. 65,240), while 2-chloro-5-nitropyridine with sodium sulphite in aqueous methyl alcohol affords 5-nitro-2-methoxypyridine and not the expected product (Caldwell and Kornfeld, *loc. cit.*). It was then conclusively shown that displacement of the methylsulphonyl group in applying the orthodox Pinner process to (VI) had taken place during the second phase of the reaction by the successful preparation of 6-*methylsulphonylnicotinamidine hydrochloride* (XVI), with no evidence of simultaneous formation of (XIV), by avoiding the use of free ammonia following the technique of Barber and Slack (*J. Amer. Chem. Soc.*, 1944, **66**, 1607).

Access to a series of aminopyridyl alkyl thioethers was obtained through *S*-(5-nitro-2-pyridyl)thiouronium chloride and 5-nitro-2-mercaptopyridine (XVII). The latter, which need not be isolated, was alkylated with the appropriate alkyl halides to give 5-*nitro*-2-*methylthio*- (XVIII), -2-*ethylthio*- (XIX), -2-n-*propylthio*- (XX), and -2-n-*butylthio*-*pyridine* (XXI); these were reduced with tin and hydrochloric acid to give the corresponding 5-*amino*-2-*methylthio*- (XXII), -2-*ethylthio*- (XXIII), -2-n-*propylthio*- (XXIV), and -2-n-*butylthio*-*pyridine* (XXV), which were further characterised, apart from (XXII), as *hydrochlorides*. The thioethers (XVIII) and (XXI) were oxidised with potassium permanganate to (XV) and 5-*nitro*-2-n-

butylsulphonylpyridine (XXVI) respectively and these, on catalytic reduction, afforded *5-amino-2-methylsulphonyl-* (XXVII) and *-2-n-butylsulphonyl-pyridine* (XXVIII). Reaction between (II) and the appropriate alkoxides readily yielded *5-cyano-2-methoxy-* (XXIX) and *-2-n-butoxy-pyridine* (XXX), which by the normal process of amidine formation, afforded (XIV)*-hydrochloride* and *6-n-butoxynicotinamidine hydrochloride* (XXXI); catalytic reduction gave *5-(2-methoxypyridyl)-* (XXXII) and *5-(2-n-butoxypyridyl)-methylamine hydrochloride* (XXXIII). (XXXI) and (XXXIII) were prepared for the specific purpose of comparison with 5-amino-2-butoxypyridine, the marked antitubercular action of which, first reported by Feinstone (*Proc. Soc. Exp. Biol. Med.*, **1946**, **63**, 153), has been confirmed under certain conditions in this laboratory (Forrest, Hart, and Walker, *Nature*, **1947**, **160**, 94).

Tests for *in vitro* antibacterial activity were kindly carried out on the substances described in the present paper by Drs. A. T. Fuller and P. D'Arcy Hart. The over-all result of these tests was to indicate that the pyridine analogues were markedly inferior in activity to the corresponding benzenoid compounds. For example, (XVI) and (XIII) had only about 1% of the antibacterial activity of the corresponding highly active benzene analogues, *p*-methylsulphonyl- and *p*-methylthio-benzamidine hydrochloride (*J.*, **1945**, 633), and (XXVII) had about a quarter of the activity of the similarly substituted benzene derivative (*ibid.*, p. 630). The more significant antibacterial titres are recorded in the Table and the feature which emerges

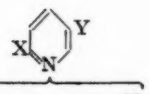


(XVI) A = SO_2; B = $C(NH_2){:}NH_2$}Cl
(XIII) A = S; B = $C(NH_2){:}NH_2$}Cl
(XXVII) A = SO_2; B = NH_2

is the high activity of the thiols and also that of (III). *p*-Aminothiophenol has been shown by Green and Bielschowsky (*Brit. J. Exp. Path.*, **1942**, **23**, 13) to have marked antibacterial activity *in vitro* but to be less active than the corresponding disulphide; this observation is difficult to understand since bacterial cultures are usually strongly reducing systems and the latter would be expected to suffer reduction to the former therein. As the antibacterial activity

Antibacterial activity in vitro.

Minimal inhibiting concentrations in mg. of drug per 100 c.c. of culture medium.



	X	Y.	Organism.	* *Strep. hæmolyt.*		* *Staph. aureus.*	* *Bact. coli.*	* *Cl. welchii.*	† *Myc. tuberculosis.*	† *Myc. phlei.*
			Medium.	a.	b.	a.	a.	a.	c.	d.
(III)	S·$C(NH_2){:}NH_2$}Cl	CN		2	50	2	10	100	2·5	—
(IV)	SH	CN		1	>100	2	20	5	1·3	—
(V)	CH_3S	CN		200	200	>200	>200	100	—	20
(II)	Cl	CN		>200	>200	>200	>200	200	—	20
(VI)	CH_3SO_2	CN		50	50	100	50	50	20	—
(VIII)	S·$C(NH_2){:}NH_2$}Cl	$CO{\cdot}NH_2$		10	500	200	500	1000	20	—
(IX)	SH	$CO{\cdot}NH_2$		1	>50	>50	>50	50	—	—
(X)	CH_3S	$CO{\cdot}NH_2$		5	200	>200	>200	200	—	—
(XXXIV)[e]	SH	NH_2		1	>50	2	10	75	20	
(XXII)	CH_3S	NH_2		200	>200	500	500	200	20	0·6
(XXIV)	C_3H_7S	NH_2		50	200	150	200	500	20	
(XXV)	C_4H_9S	NH_2		50	200	50	100	200	20	
(XII)	SH	$C(NH_2){:}NH_2$}Cl		10	100	50	80	500	20	
(XXXI)	C_4H_9O	$C(NH_2){:}NH_2$}Cl		10	100	100	100	50	20	
(XXXIII)	C_4H_9O	$CH_2{\cdot}NH_3$}Cl		50	50	200	200	100	20	
(XXXV)[f]	SH	H		2	100	20	20	1000	20	

* Tests by Dr. A. T. Fuller.
† Tests by Dr. P. D'Arcy Hart.
— Not active at 20 mg./100 c.c.
a Nutrient broth.
b Blood.
c Albumin " Tween 80 " (Dubos) and albumin (Dubos).
d Broth (surface culture).
e Prepared following Rath (*loc. cit.*).
f Prepared following Phillips and Shapiro (*J.*, **1942**, 584).

in both cases was counteracted by *p*-aminobenzoic acid it is not easy to decide how much, if any, of the net observed activity was contributed by the thiol or disulphide group, and how

much of the activity was of the " sulphonamide " type; on the other hand, the disulphide was inhibited in the presence of blood, plasma, or as little as 5% of serum. Similarly, the thiols described in the present paper showed reduced activity in the presence of blood. A number of thiols and disulphides in the thiazole series have been shown to possess antibacterial activity *in vitro* (Gibbs and Robinson, *J.*, 1945, 925) and the activity was ascribed to the thiol and disulphide group in these cases, while 3 : 3′-dipyridyl disulphide has been claimed as an antibacterial agent (B.P. 582,638); the degree of activity of these compounds appears to be comparable with, or slightly higher than, that of (III), (IX), 5-amino-2-mercaptopyridine (XXXIV), or 2-mercaptopyridine (XXXV), as far as comparison between tests carried out in one laboratory and those carried out in another allows. Replacement of the amino-group in 5-amino-2-butoxypyridine by the amidine group, in (XXXI), or by the aminomethyl group, in (XXXIII), reduced antitubercular activity markedly.

Experimental.

6-Chloronicotinamide (I).—Methyl coumalate (50 g.), prepared in one operation from malic acid following Ruzicka's technique for the ethyl ester (*Helv. Chim. Acta*, 1921, **4**, 504), was converted into 6-hydroxynicotinic acid (36·2 g.) according to v. Pechmann and Welsh (*Ber.*, 1884, **17**, 2391). The latter, m. p. 303°, was of adequate purity for the next stage, which has advantages over the method described by Mills and Widdows (*J.*, 1908, **93**, 1379). 6-Hydroxynicotinic acid (30 g.) was treated cautiously with phosphoryl chloride (50 c.c.) and the mixture heated for 2½ hours on the water-bath. Excess phosphoryl chloride was removed under reduced pressure and the resulting brown gum was dissolved in acetone (50 c.c.) and added slowly to cooled aqueous ammonia (100 c.c.; *d* 0·88). After standing for 30 minutes, the mixture was diluted with water and the crude product collected. Recrystallisation from spirit (norite) afforded colourless rectangular plates (26·6 g.), m. p. 208° (Found: C, 46·2; H, 3·1. Calc. for $C_6H_5ON_2Cl$: C, 46·0; H, 3·2%). Rath (*loc. cit.*) records m. p. 205° and Mills and Widdows (*loc. cit.*) record m. p. 211°.

2-Chloro-5-cyanopyridine (II).—6-Chloronicotinamide (30 g.) was refluxed with phosphoryl chloride (75 c.c.) in chloroform (250 c.c.) for 2½ hours. Solvent and excess phosphoryl chloride were removed by distillation and the residue was treated with melting ice, the resulting precipitate being collected. Crystallisation from spirit afforded colourless hexagonal plates (24 g.), m. p. 117—118° (Found: C, 52·0; H, 2·4. Calc. for $C_6H_3N_2Cl$: C, 52·0; H, 2·2%). Rath (*loc. cit.*) records m. p. 115°.

S-(5-Cyano-2-pyridyl)thiouronium Chloride (III).—2-Chloro-5-cyanopyridine (21·6 g.) was added to a warm solution of thiourea (12 g.) in absolute alcohol (200 c.c.) and the mixture was refluxed for 2 hours. The product (32 g., m. p. 190—192°), which separated on cooling, was collected. The *compound* crystallised from absolute alcohol in thin yellow prisms with pointed ends, m. p. 192° (Found: C, 39·1; H, 2·9; N, 26·4. $C_7H_6N_4S,HCl$ requires C, 39·1; H, 3·2; N, 26·1%).

5-Cyano-2-mercaptopyridine (IV).—*S*-(5-Cyano-2-pyridyl)thiouronium chloride (9·8 g.) was shaken with 2N-aqueous sodium hydroxide (25 c.c.) for about 15 minutes. A further quantity of 2N-sodium hydroxide (25 c.c.) was added and the solution was filtered and acidified with acetic acid, affording a pure product in practically quantitative yield. The substance separated from a large volume of alcohol in long yellow needles, m. p. 255° (Found: C, 53·3; H, 3·1. Calc. for $C_6H_4N_2S$: C, 53·0; H, 2·9%). Rath (*loc. cit.*) records m. p. 252° and U.S.P. 1,753,658 records m. p. 245°.

5-Cyano-2-methylthiopyridine (V).—(*a*) 5-Cyano-2-mercaptopyridine (0·34 g.) was dissolved in N-sodium hydroxide (2·5 c.c.) and treated with methyl iodide (0·35 c.c.). Alcohol was added to homogeneity and the solution was kept at room temperature for 12 hours. The crystalline product (0·32 g.) was collected. The *compound* separated from 50% alcohol in colourless needles, m. p. 78° (Found: C, 56·2; H, 4·0; N, 18·5. $C_7H_6N_2S$ requires C, 56·0; H, 4·0; N, 18·7%).

(*b*) *S*-(5-Cyano-2-pyridyl)thiouronium chloride (11 g.) was shaken with N-sodium hydroxide (51 c.c.) for 30 minutes. An equal volume of N-sodium hydroxide was added, and the solution was filtered and treated with methyl iodide (7·2 g.) and a little alcohol. There was a slight rise in temperature and a rapid separation of crystals took place. After standing overnight the product, m. p. 76—78°, was collected; the yield was quantitative.

5-Cyano-2-methylsulphonylpyridine (VI).—(*a*) 5-Cyano-2-methylthiopyridine (9 g.) was dissolved in acetone (60 c.c.) and 2N-sulphuric acid (100 c.c.) was added. Aqueous potassium permanganate solution (12·6 g. in 250 c.c.) was then run into the stirred mixture over a period of 30 minutes, a slight rise in temperature being observed. Manganese dioxide was thereafter destroyed with sulphur dioxide and the product (5·1 g., m. p. 131—133°) was collected, a further quantity (5·4 g.) being obtained on concentrating the filtrate. Crystallisation from absolute alcohol afforded the *cyano-sulphone* in the form of colourless needles (9·5 g.), m. p. 133° (Found: C, 46·2; H, 3·5; N, 15·4. $C_7H_6O_2N_2S$ requires C, 46·2; H, 3·3; N, 15·4%).

Further examination of the oxidation mother-liquors afforded a small amount of impure 6-methylsulphonylnicotinamide.

(*b*) 6-Methylsulphonylnicotinamide (3 g.) (see below) was treated with phosphoryl chloride (7 c.c.) in chloroform (25 c.c.) and the suspension was refluxed for 3 hours. The reaction mixture was worked up in the usual way, the residue being crystallised from absolute alcohol to give the cyano-sulphone (2·16 g.), m. p. and mixed m. p. 133°.

S-(5-Carbamyl-2-pyridyl)thiouronium Chloride (VIII).—6-Chloronicotinamide (33·5 g.), thiourea (17·7 g.), and absolute alcohol (350 c.c.) were heated on the water-bath under reflux for 6 hours, when a gradual separation of crystals and colouring of the solution occurred. After cooling, the product (46·4 g., m. p. 195°) was collected and a further quantity (1·2 g.) was obtained from the filtrate. The

compound separated from glacial acetic acid in pale yellow needles, m. p. 195° (Found: N, 23·8. $C_7H_8ON_4S,HCl$ requires N, 24·1%).

6-*Mercaptonicotinamide* (IX).—The preceding thiouronium salt (2·8 g.) was decomposed with 2N-sodium hydroxide, following the technique used in the analogous case described above, and the product (1·5 g.) was isolated in the normal way. The *thiol* crystallised from a large volume of water in pale yellow needles, m. p. 266—268° (Found: C, 46·8; H, 3·6. $C_6H_6ON_2S$ requires C, 46·7; H, 3·9%).

6-*Methylthionicotinamide* (X).—*S*-(5-Carbamyl-2-pyridyl)thiouronium chloride (29 g.) was decomposed with alkali and the resulting thiol methylated directly. The *product* (16·4 g.) separated from water in colourless needles, m. p. 166—167° (Found: C, 50·0; H, 4·8; N, 17·0. $C_7H_8ON_2S$ requires C, 50·0; H, 4·8; N, 16·7%).

6-*Methylsulphonylnicotinamide* (VII).—(*a*) 6-Methylthionicotinamide (6 g.), suspended in a mixture of acetone (40 c.c.) and excess of 2N-sulphuric acid, was oxidised with aqueous potassium permanganate (7·6 g. in 150 c.c.) and the product (6·9 g.) collected. The *compound* separated from 80% alcohol in rectangular plates, m. p. 210° (Found: C, 42·2; H, 3·9; N, 13·9. $C_7H_8O_3N_2S$ requires C, 42·0; H, 4·0; N, 14·0%).

(*b*) 6-Methylthionicotinamide (2 g.) in acetone (10 c.c.) was treated cautiously with 30% hydrogen peroxide (6 c.c.) and the mixture was then heated on the water-bath for 3 hours After concentration and cooling, the product (2·03 g.) was collected. As the m. p. was not sharp the product was re-treated with hydrogen peroxide under the same conditions and again isolated. Recrystallisation from 80% alcohol afforded clusters of colourless needles, m. p. 224—226°, depressed on admixture with the sulphone prepared in (*a*) (above). Analysis showed the substance to be the sulphoxide, 6-*methylsulphinylnicotinamide* (XI) (Found: C, 45·7; H, 4·6; N, 15·0. $C_7H_8O_2N_2S$ requires C, 45·6; H, 4·3; N, 15·2%), which gave the sulphone, m. p. and mixed m. p. 209—210°, on further oxidation with potassium permanganate.

6-*Mercaptonicotinamidine Hydrochloride* (XII).—5-Cyano-2-mercaptopyridine (5 g.), chloroform (13 c.c.), and absolute alcohol (6 c.c.) were mixed and saturated at 0° with dry hydrogen chloride. After standing at 0° for 60 hours, solvent and excess hydrogen chloride were removed in a vacuum and the yellow powdery residue was kept for 5 days at 37° in contact with 10% alcoholic ammonia (70 c.c.). The solid product from this stage was mixed with the residue obtained by evaporation of the alcoholic ammonia and the bulked material was crystallised from a large volume of water, affording two crops (2·6 g. and 0·35 g.) of unchanged starting material, followed by the desired amidine hydrochloride (1·07 g.). The *compound* separated from a small volume of water in yellow needles, m. p. 290°, but did not give precise analytical figures (Found: C, 38·5; H, 3·3; N, 22·6. $C_6H_7N_3S,HCl$ requires C, 38·0; H, 4·2; N, 22·2%). The *benzoate*, obtained by double decomposition in aqueous solution, separated from water in yellow plates, m. p. 266° (decomp.), giving precise analytical figures (Found: C, 56·6; H, 4·7; N, 15·1. $C_6H_7N_3S,C_7H_6O_2$ requires C, 56·7; H, 4·7; N, 15·3%).

Attempts to increase the extent of the conversion of nitrile by the use of larger volumes of chloroform, or of dioxan, were ineffective.

6-*Methylthionicotinamidine Benzoate* (XIII).—5-Cyano-2-methylthiopyridine (5 g.), dry dioxan (25 c.c.), and methyl alcohol (1·3 c.c.) were mixed and saturated at 0° with dry hydrogen chloride and the mixture was kept for 10 days in the refrigerator. Crude imino-ether hydrochloride, freed from solvent and excess hydrogen chloride in a vacuum, was treated with saturated methyl alcoholic ammonia (75 c.c.) at 37° for 7 days. The solution was evaporated to dryness, the residue taken up in water, brought to pH 5 with hydrochloric acid, and filtered from unchanged nitrile (2·8 g.). On evaporating the aqueous solution to dryness the resulting syrupy hydrochloride could not be induced to crystallise. The *benzoate*, however, obtained by double decomposition in aqueous solution, separated from water in rectangular plates, m. p. 248°, softening at 236° (Found: C, 58·0; H, 5·3; N, 14·5. $C_7H_9N_3S,C_7H_6O_2$ requires C, 58·1; H, 5·2; N, 14·5%). The *acetate*, similarly prepared, crystallised from water in colourless needles, m. p. 224—226° (Found: N, 18·1. $C_7H_9N_3S,C_2H_4O_2$ requires N, 18·5%).

A number of modifications of the above experiment were tried but none gave any greater conversion of nitrile.

Attempted Preparation of 6-*Methylsulphonylnicotinamidine Hydrochloride. Formation of* 6-*Methoxynicotinamidine* (XIV).—5-Cyano-2-methylsulphonylpyridine (6·06 g.), methyl alcohol (1·3 c.c.), and dioxan (25 c.c.) were treated for 6 days at 0° with dry hydrogen chloride (3·5 g.), and the crude imino-ether hydrochloride was set aside with saturated methyl-alcoholic ammonia (70 c.c.) at 37° for 4 days. The ammoniacal solution was evaporated to dryness and the residue was taken up in water, adjusted to pH 5—6, and filtered from a small quantity (0·5 g.) of 5-cyano-2-methoxypyridine, identified by comparison with an authentic specimen (see below), m. p. and mixed m. p. 94°. The crude amidine hydrochloride (5 g.), obtained by evaporating the filtrate to dryness and extraction from ammonium chloride with absolute alcohol, showed no tendency to crystallise. The *benzoate*, obtained by double decomposition in aqueous solution, however, separated from water in rectangular plates, m. p. 253° (Found: C, 61·2; H, 5·4; N, 15·6. $C_7H_9ON_3,C_7H_6O_2$ requires C, 61·5; H, 5·5; N, 15·4%); the analytical figures indicated the substance to be 6-methoxynicotinamidine benzoate, and no depression of the m. p. was observed on admixture with an authentic specimen (see below).

Similarly, the *acetate*, prepared by double decomposition, separated from water in colourless needles, m. p. 246—248°, not depressed on admixture with an authentic specimen of 6-methoxynicotinamidine acetate (Found: C, 50·9; H, 6·2; N, 19·7. $C_7H_9ON_3,C_2H_4O_2$ requires C, 51·2; H, 6·2; N, 19·9%).

6-*Methylsulphonylnicotinamidine Hydrochloride* (XVI).—5-Cyano-2-methylsulphonylpyridine (5 g.) was converted into crude imino-ether hydrochloride in the usual way during 12 days at 0°. After removal of the solvent (dioxan) and excess hydrogen chloride, the free imino-ether base was liberated with ice-cold 0·5N-sodium carbonate (100 c.c.) and extracted with ice-cold chloroform. The extract was washed with water and evaporated in a vacuum. The residue was dissolved in warm alcohol (75 c.c.) and treated with aqueous ammonium chloride solution (1·6 g. in 25 c.c.) at 37° for 60 hours. Unchanged ammonium chloride (0·25 g.) was precipitated with acetone at 0° and the filtrate was evaporated to dryness. Unchanged starting material (1·05 g.) remained undissolved on extracting the residue with water and the aqueous solution was taken to complete dryness. The *amidine hydrochloride* was

extracted with hot absolute alcohol and then crystallised from a very small volume of water, when colourless rectangular plates (2·2 g.) separated, m. p. 238° (Found : N, 17·9. $C_7H_9O_2N_3S,HCl$ requires N, 17·8%).

The *benzoate* separated from water in long rectangular plates, m. p. 210° (Found : C, 52·3; H, 4·6; N, 13·0. $C_7H_9O_2N_3S,C_7H_6O_2$ requires C, 52·3; H, 4·7; N, 13·1%). The *acetate* crystallised from water in fine needles, m. p. 196—198° (Found : N, 15·9. $C_7H_9O_2N_3S,C_2H_4O_2$ requires N, 16·2%).

Action of Methyl-alcoholic Ammonia on 5-Nitro-2-methylsulphonylpyridine. Formation of 5-Nitro-2-amino- and 5-Nitro-2-methoxy-pyridine.—5-Nitro-2-methylsulphonylpyridine (5 g.) was kept at 37° for 4 days with 14% methyl-alcoholic ammonia (70 c.c.) in a pressure bottle. The mixture was evaporated to dryness and the residue was crystallised from alcohol, affording 5-nitro-2-aminopyridine (2·35 g.), m. p. 184° alone and in admixture with an authentic specimen (Found : N, 30·2. Calc. for $C_5H_5O_2N_3$: N, 30·2%). On steam-distillation of the mother-liquors a colourless solid (0·4 g.) separated in the distillate and was collected; this substance was shown by m. p. and mixed m. p. (110°) to be 5-nitro-2-methoxypyridine (Found : N, 18·2. Calc. for $C_6H_6O_3N_2$: N, 18·2%). Finally, a further quantity (0·85 g.) of 5-nitro-2-aminopyridine was obtained from the steam-distillation still-residue.

5-Nitro-2-mercaptopyridine (XVII).—*S*-(5-Nitro-2-pyridyl)thiouronium chloride (23·4 g.) (Surrey and Lindwall, *J. Amer. Chem. Soc.*, 1940, **62**, 1697) was suspended in water (50 c.c.) and 2N-sodium hydroxide (50 c.c.) was run into the stirred mixture. Stirring was continued for 15 minutes and the dark red suspension was then heated on the water-bath for 5 minutes to complete the decomposition of the thiouronium salt. A further quantity (50 c.c.) of 2N-sodium hydroxide was added, and the solution, filtered from some 5 : 5′-dinitro-2 : 2′-dipyridyl disulphide (1·2 g., m. p. 132—135°), gave the thiol (14·2 g.), m. p. 186—188°, on acidification with concentrated hydrochloric acid. Caldwell and Kornfeld (*loc. cit.*) record m. p. 188—191°.

5-Nitro-2-methylthiopyridine (XVIII).—*S*-(5-Nitro-2-pyridyl)thiouronium chloride (46·8 g.) was suspended in water (100 c.c.) and decomposed with two successive portions of 2N-sodium hydroxide (each 100 c.c.) in the manner described above. The solution, filtered from disulphide (2 g.), was heated on the water-bath with methyl iodide (29 g.) and absolute alcohol (30 c.c.) until the colour practically disappeared (*ca.* 15 minutes). The product was collected after cooling. The *compound* separated from spirit in pale yellow rectangular plates (31·7 g.), m. p. 115° (Found : N, 16·2. $C_6H_6O_2N_2S$ requires N, 16·5%).

5-Nitro-2-ethylthiopyridine (XIX).—Obtained in a similar manner in 91% yield using ethyl iodide, the *compound* crystallised from methyl alcohol in yellow rectangular plates, m. p. 60° (Found : N, 15·1. $C_7H_8O_2N_2S$ requires N, 15·2%).

5-Nitro-2-n-propylthiopyridine (XX).—Obtained in 91% yield using *n*-propyl iodide, the *compound* was obtained as a yellow oil, b. p. 116°/0·5 mm. (Found : N, 14·0. $C_8H_{10}O_2N_2S$ requires N, 14·1%).

5-Nitro-2-n-butylthiopyridine (XXI).—Obtained in 87% yield using *n*-butyl iodide, the *compound* was obtained as a yellow oil, b. p. 140°/1 mm. (Found : C, 51·3; H, 5·6. $C_9H_{12}O_2N_2S$ requires C, 50·9; H, 5·7%).

5-Nitro-2-methylsulphonylpyridine (XV).—5-Nitro-2-methylthiopyridine (12 g.) was treated with potassium permanganate using the technique described above for analogous oxidations. The *sulphone* separated from absolute alcohol in colourless rhombs (13·3 g.), m. p. 115° (Found : N, 13·9. $C_6H_6O_4N_2S$ requires N, 13·9%). The m. p. was depressed to 95° on admixture with the starting material.

5-Nitro-2-n-butylsulphonylpyridine (XXVI).—5-Nitro-2-*n*-butylthiopyridine (15·5 g.) was oxidised in the same manner. The *sulphone* was isolated as an oil (15·6 g.), b. p. 182°/0·5 mm., which solidified in the receiver; it then crystallised from a very small volume of methyl alcohol in elongated pale yellow plates, m. p. 58° (Found : N, 11·5. $C_9H_{12}O_4N_2S$ requires N, 11·5%).

5-Amino-2-methylthiopyridine (XXII).—5-Nitro-2-methylthiopyridine (5 g.) was reduced with granulated tin (7 g.) and 15% hydrochloric acid (36 c.c.) on the water-bath for an hour. The mixture was cooled, saturated with hydrogen sulphide, and filtered. The *amine*, isolated by addition of excess caustic alkali and extraction with ether, separated from benzene–ligroin in light brown needles (2·42 g.), m. p. 71—72° (Found : N, 20·1. $C_6H_8N_2S$ requires N, 20·0%).

5-Amino-2-ethylthiopyridine (XXIII).—5-Nitro-2-ethylthiopyridine (5 g.) was reduced in the same manner. The *amine* distilled as a viscous yellow oil (3 g.), b. p. 126°/1 mm. (Found : N, 17·9. $C_7H_{10}N_2S$ requires N, 18·1%). The *dihydrochloride*, obtained by dissolving the base in the calculated amount of alcoholic hydrochloric acid, separated from absolute alcohol in small blunt needles, m. p. 175—176° (Found : N, 12·6. $C_7H_{10}N_2S,2HCl$ requires N, 12·4%).

5-Amino-2-n-propylthiopyridine (XXIV).—5-Nitro-2-*n*-propylthiopyridine (7·5 g.) similarly afforded the *amine* as a viscous yellow oil (3·6 g.), b. p. 142°/1 mm. (Found : N, 16·5. $C_8H_{12}N_2S$ requires N, 16·7%). The *hydrochloride* crystallised from alcohol in rectangular plates, m. p. 154° (Found : N, 13·3. $C_8H_{12}N_2S,HCl$ requires N, 13·6%).

5-Amino-2-n-butylthiopyridine (XXV).—In this case the lower solubility of 5-nitro-2-*n*-butylthiopyridine (5 g.) in the reducing mixture necessitated the addition of an equal volume of glacial acetic acid. The *amine* was obtained as a pale yellow oil (2·8 g.), b. p. 184°/10 mm. (Found : C, 59·6; H, 7·8. $C_9H_{14}N_2S$ requires C, 59·3; H, 7·7%).

Neutralisation with the calculated volume of alcoholic hydrochloric acid afforded the *dihydrochloride*, which separated from methyl alcohol–ethyl acetate in clusters of colourless needles, m. p. 139—141° (Found : N, 11·4. $C_9H_{14}N_2S,2HCl$ requires N, 11·0%). Repeated recrystallisation from the same solvent mixture caused hydrolysis to the *monohydrochloride* with fall in m. p. to 128—129° (Found : N, 12·6. $C_9H_{14}N_2S,HCl$ requires N, 12·8%).

5-Amino-2-methylsulphonylpyridine (XXVII).—5-Nitro-2-methylsulphonylpyridine (5 g.) was reduced at room temperature in methyl alcohol (200 c.c.) in the presence of palladised strontium carbonate (2 g.) with hydrogen at an initial pressure of 24 lbs./sq. in. Hydrogenation was complete in less than an hour. The *aminosulphone* crystallised from water in colourless leaflets, m. p. 171—173°, softening at 165° (Found : N, 16·3. $C_6H_8O_2N_2S$ requires N, 16·3%).

5-Amino-2-n-butylsulphonylpyridine (XXVIII).—When 5-nitro-2-*n*-butylsulphonylpyridine (5 g.)

was hydrogenated in the same way at 48 lbs./sq. in. pressure of hydrogen, reduction was complete in 10 minutes. The *amino-sulphone* separated from alcohol in colourless rhombs (4·2 g.), m. p. 97° (Found: N, 13·1. $C_9H_{14}O_2N_2S$ requires N, 13·1%).

5-Cyano-2-methoxypyridine (XXIX).—A solution of 2-chloro-5-cyanopyridine (13·9 g.) in a mixture of dioxan (50 c.c.) and methyl alcohol (50 c.c.) was added to a methyl-alcoholic solution of sodium methoxide (2·3 g. of sodium) and the mixture was refluxed for 30 minutes. After cooling, sodium chloride was removed and the filtrate was evaporated. The *compound* separated from absolute alcohol in colourless rectangular plates (12 g.), m. p. 94° (Found: N, 21·1. $C_7H_6ON_2$ requires N, 20·9%).

5-Cyano-2-n-butoxypyridine (XXX).—2-Chloro-5-cyanopyridine (13·9 g.) was similarly treated with sodium *n*-butoxide in *n*-butyl alcohol–dioxan. The *compound* was isolated as an oil, b. p. 140—150°/15 mm., which solidified on cooling to a mass of colourless needles, m. p. 24° (Found: C, 67·8; H, 6·8; N, 15·7. $C_{10}H_{12}ON_2$ requires C, 68·2; H, 6·8; N, 15·9%).

6-Methoxynicotinamidine (XIV) *Hydrochloride*.—Crude imino-ether hydrochloride, prepared by treating 5-cyano-2-methoxypyridine (4·5 g.) with dry hydrogen chloride (4 g.) at 0° for 7 days in dioxan–methyl alcohol, was incubated with methyl-alcoholic ammonia (70 c.c.) at 37° for 4 days. On processing the product, unchanged starting material (1·9 g., m. p. and mixed m. p. 94°) was first recovered. Exhaustive evaporation and extraction with alcohol then gave a stiff residue (3·4 g.), which eventually crystallised. The *hydrochloride* separated, with considerable losses, from a small volume of methyl alcohol in colourless needles, m. p. 278—280° (Found: N, 22·4. $C_7H_9ON_3$,HCl requires N, 22·4%).

The benzoate, m. p. 253°, and the acetate, m. p. 246—248°, both prepared by double decomposition in aqueous solution, were identical with the corresponding salts of the amidine derived from 5-cyano-2-methylsulphonylpyridine by the orthodox Pinner technique (see above).

5-(2-Methoxypyridyl)methylamine Hydrochloride (XXXII).—5-Cyano-2-methoxypyridine (5 g.) was reduced in methyl-alcoholic ammonia (100 c.c.) in the presence of Raney nickel (2 g.) at an initial hydrogen pressure of 42 lbs./sq. in. Reduction was complete in an hour. After removal of catalyst and solvents, the base was neutralised with one equivalent of alcoholic hydrochloric acid. The *hydrochloride* separated from spirit in colourless rectangular plates, m. p. 216—218° (Found: N, 15·8. $C_7H_{10}ON_2$,HCl requires N, 16·0%).

6-n-*Butoxynicotinamidine Hydrochloride* (XXXI).—5-Cyano-2-*n*-butoxypyridine (7·6 g.) was treated with methyl alcohol (1·6 g.) and dry hydrogen chloride (5 g.) in dioxan (25 c.c.) at 0° for 7 days. The crude imino-ether hydrochloride was incubated with methyl-alcoholic ammonia (70 c.c.) at 37° for 4 days. On working up in the usual way, 6-n-*butoxynicotinamide* was first isolated, separating from spirit in clusters of colourless needles (1·5 g.), m. p. 158° (Found: N, 14·6. $C_{10}H_{14}O_2N_2$ requires N, 14·4%). The residue (6·5 g.), obtained on exhaustive evaporation and extraction with absolute alcohol, was crystallised from 1½ parts of water affording colourless irregular plates of the *hydrochloride monohydrate*, m. p. 95° (Found: N, 16·8; loss of weight at 100° in a vacuum, 7·0. $C_{10}H_{15}ON_3$,HCl,H_2O requires N, 16·9; H_2O, 7·3%).

The *benzoate* separated from water in colourless rectangular plates, m. p. 228° (Found: C, 64·7; H, 6·5; N, 13·2. $C_{10}H_{15}ON_3$,$C_7H_6O_2$ requires C, 64·8; H, 6·7; N, 13·0%).

5-(2-n-Butoxypyridyl)methylamine Dihydrochloride (XXXIII).—Hydrogenation of 5-cyano-2-*n*-butoxypyridine was carried out in the same manner as described above for the analogous methoxy-compound. The monohydrochloride did not separate on the addition of one equivalent of alcoholic hydrochloric acid but the addition of a further equivalent afforded the *dihydrochloride*, which separated from *iso*propyl alcohol in colourless rectangular plates, m. p. 228° (Found: N, 12·8. $C_{10}H_{16}ON_2$,2HCl requires N, 12·9%).

The authors are greatly indebted to Drs. A. T. Fuller and P. D'Arcy Hart for their kindness in carrying out antibacterial tests on the substances described in this communication, and to Messrs. May and Baker Limited for a gift of 2-aminopyridine.

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394. *Curare Alkaloids. Part VIII. Examination of Commercial Curare,* Chondrodendron tomentosum *R and P and* Anomospermum grandifolium *Eichl.*

By Harold King.

The aim of the present investigation was primarily the determination of the botanical source of *dextro*tubocurarine chloride on account of the use of the latter as an adjunct in anæsthesia. A bush-rope from northern Peru has now given *dextro*tubocurarine chloride and four non-quaternary bases of which *dextro*tomentocurine is new. A commercial curare from southern Peru also prepared from *Ch. tomentosum* has likewise given *dextro*tubocurarine chloride and four non-quaternary alkaloids. These results are in conflict with the results obtained in Part VI where *Ch. tomentosum* from northern Peru gave *lævo*tubocurarine chloride. A botanically undifferentiated species may be involved.

Anomospermum grandifolium which has a reputation as a constituent of curare has been examined. It contained a quaternary fraction with a curare-action.

In Part I (King, *J.*, 1935, 1381) it was shown that the active principle of tube-curare was *dextro*tubocurarine chloride. Since that time this substance has found important application

as an adjunct in surgical anæsthesia, and to ensure supplies of this drug it was essential to identify the plant which produced this alkaloid. It was known that tube-curare came from the region of the upper waters of the Amazon in Peru and from the chemical relationship established between *dextro*tubocurarine chloride and bebeerine it was thought that the genus *Chondrodendron* was involved.

In Part VI (King, *J.*, **1947**, **936**) an account was given of the chemical examination of stems of *Chondrodendron tomentosum* collected near Tarapoto, in northern Peru. Leaves which were collected at the same time were found by Mr. N. Y. Sandwith, M.A., of The Herbarium, Kew to be indistinguishable from authentic leaves of this species. On chemical examination the stems yielded *lævo*bebeerine (*lævo*curine), a tertiary alkaloid found accompanying *dextro*-tubocurarine chloride in tube-curare, and *lævo*tubocurarine chloride.

Dutcher (*J. Amer. Chem. Soc.*, **1946**, **68**, **419**), however, from a sample of curare prepared by Indians of the upper Amazon under the supervision of a botanist-explorer who identified the plant used as *Chondrodendron tomentosum*, isolated four tertiary alkaloids, *dextroiso*chondrodendrine, *dextroiso*chondrodendrine dimethyl ether, *lævo*bebeerine, and *dextro*chondrocurine. The quaternary alkaloid proved to be *dextro*tubocurarine chloride.

Thus the plant *Chondrodendron tomentosum* has on one occasion given *lævo*tubocurarine chloride and on another the *dextro*-alkaloid. Similarly the *radix pareiræ bravæ* of pharmacy sometimes yielded *dextro*bebeerine and at other times *lævo*bebeerine. It was found (King, *J.*, **1940**, **737**) that when *pareira brava* gave *lævo*bebeerine it came from *Chondrodendron platyphyllum* and when it gave *dextro*bebeerine from *Ch. microphyllum*. It seems very probable therefore that two species are involved under the name *Ch. tomentosum* and it is only right to add that my adviser on botanical matters, Mr. Sandwith, has always emphasised that final and conclusive identification of a species cannot be made on sterile botanical specimens, that is on specimens without flowers. On the present evidence another and possibly new *Chondrodendron* species must be implicated but whether it yields *dextro*- or *lævo*-tubocurarine chloride must for the present remain undetermined.

Since the above results were obtained, further material has been received from Peru and its examination is the subject of this communication.

To meet the demand for *dextro*tubocurarine chloride, the firm of Asher, Kates y Cia, S.A., of Lima, Peru, collect the stems of a bush-rope which grows in the region of the Madre de Dios River, in the province of Cuzco, Peru, and make a concentrated extract. This firm kindly supplied me with leaves of the plant they use and these were identified by Mr. Sandwith as being indistinguishable from *Ch. tomentosum*. A sample of the crude concentrated extract furnished *dextro*tubocurarine chloride, isolated by use of ammonium reineckate by Kapfhammer's process so as to avoid the strongly acid solutions involved in the mercuric chloride process. The non-quaternary alkaloids were separated by a method depending on their different basicities (see King and Ware, *J.*, **1941**, **331**) into the four alkaloids, *iso*chondrodendrine dimethyl ether, *lævo*bebeerine, *dextro*chondrocurine, and *dextroiso*chondrodendrine, the basicity increasing in the order given. It is of interest that these five alkaloids are the same as those found by Dutcher (*loc. cit.*) who separated the non-quaternary ones by chromatography. It is possible that Dutcher's starting material came from the same region as this commercial extract as the term Upper Amazon used by Dutcher would cover the Madre de Dios River.

Through the kind co-operation of Mr. J. W. Massey, of the British Consulate at Iquitos in northern Peru, I received in April **1947**, a quantity of stems and leaves, collected at Sisa in the region of Tarapoto, of a bush-rope said to be used by the natives in the preparation of an arrow-poison. It will be recalled that it was from Tarapoto that the stems and leaves, identified as *Ch. tomentosum*, and which gave *lævo*tubocurarine chloride, came (see Part VI). The new material was also identified by Mr. Sandwith as being indistinguishable from *Ch. tomentosum*. Chemical examination showed the presence of five alkaloids, *dextro*tubocurarine chloride, *lævo*-bebeerine, *dextro*chondrocurine, *dextroiso*chondrodendrine, and a new alkaloid dextro*tomentocurine*. The latter is the most strongly basic of the non-quaternary alkaloids. It only occurred in very small quantity and in its properties resembled *dextroiso*chondrodendrine more closely than it did *lævo*bebeerine and *dextro*chondrocurine. A special search was made, in the non-phenolic fraction, for *iso*chondrodendrine dimethyl ether but it was not found. Four of the alkaloids agree with those found in the commercial sample of curare from the province of Cuzco and with those found by Dutcher. Two of them, *dextro*tubocurarine chloride and *lævo*bebeerine (*lævo*-curine), also agree with the alkaloidal bases found in the original tube-curare of native origin described in Part I.

It may therefore be regarded as established that from widely separated Peruvian localities a bush-rope indistinguishable from *Ch. tomentosum* yields *dextro*tubocurarine chloride. Another

bush-rope also indistinguishable as far as its leaves are concerned from *Ch. tomentosum* has yielded *lævo*tubocurarine chloride, an enantiomorph of inferior activity. It is of interest that Foster and Turner (*Quart. J. Pharm. Pharmacol.*, 1947, **20**, 228), examining commercial samples of curare purporting to yield the *dextro*-alkaloid, have on one occasion also encountered a *lævo*rotatory quaternary salt of inferior activity.

It is unlikely that further progress in unravelling this problem can be made until flowers and stems of the two species concerned can be obtained and their identity established beyond doubt.

The botanist Schwacke (*Jahrb. Kgl. bot. Gart. bot. Mus., Berlin*, 1881—4, III, 220) identified one of the ingredients of Ticuna curare as *Anomospermum grandifolium* Eichl [now known as *Elissarrhena grandifolia* (Eichl) Diels]. De Lacerda (*Arch. Mus. nac.*, Rio de Janeiro, 1901, **11**, 163) examined this species and found that a crude extract had a true curare action. Krukoff and Moldenke (*Brittonia*, 1938, **3**, 73), however, expressed their conviction that the plant identified as *Anomospermum grandifolium* by Schwacke was in reality *Chondrodendron limaciifolium*. Mr. J. W. Massey kindly sent me a quantity of leaves and stems of a liane, known in the Iquitos region as amphi-huasca (poison-rope). This was identified by Mr. N. Y. Sandwith as being indistinguishable from *Anomospermum grandifolium* Eichl. A crude extract of the stems was found by Dr. F. C. MacIntosh of this Institute to have a true curare action and when the alkaloids were separated into quaternary and non-quaternary bases the curare activity was found in the quaternary fraction. There is thus this further experimental evidence in support of the occasional use of *Anomospermum grandifolium* by the natives as an active ingredient of curare.

Experimental.

Commercial Curare from Lima, Peru.—Through the kindness of Mr. Herbert A. Berens of Biddle Sawyer & Co., a sealed sample tin of curare was obtained from Asher Kates & Co., of Lima, who supply the British and American markets with crude curare from which *dextro*tubocurarine chloride is prepared. The product, a thick black syrup weighing 84 g., was made up to 1165 c.c. with water and when assayed by Dr. F. C. MacIntosh of this Institute by the rabbit head-drop test exhibited curare activity equivalent to a 1·5% solution of *dextro*tubocurarine chloride.

Isolation of dextro*Tubocurarine Chloride.*—The solution was treated with basic lead acetate solution (250 c.c., 0·5N), the precipitate removed, and the filtrate freed from lead by hydrogen sulphide. An aliquot portion (500 c.c.) of the filtrate (2060 c.c.) was treated with sodium hydrogen carbonate (21 g.) and kept for 12 hours and then filtered from the precipitate (4·4 g.). The filtrate was extracted 6 times with chloroform which removed non-quaternary bases (1·5 g.). The extracted solution was neutralised with hydrochloric acid (30 c.c.; *d* 1·12) and treated with a saturated solution of ammonium reineckate (300 c.c.). The precipitated reineckate was collected and whilst still damp dissolved in acetone and the acetone solution treated with excess of saturated silver sulphate solution. The silver reineckate was removed and the filtrate treated carefully with barium chloride solution to remove all sulphate and silver ions. The combined solutions, from the 4 aliquot portions, on concentration, gave crude *dextro*tubocurarine chloride (6·4 g.). A portion (1·73 g.) recystallised from water gave *dextro*tubocurarine chloride (1·59 g.), $[\alpha]_D^{17°}$ +199°. Dutcher (*J. Amer. Chem. Soc.*, 1946, **68**, 421) gives $[\alpha]_D^{23°}$ +215° for the pure anhydrous salt.

*Isolation of Dimethyl*iso*chondrodendrine,* lævo*Bebeerine,* dextro*Chondrocurine, and* iso*Chondrodendrine.*—The precipitates obtained with sodium hydrogen carbonate from the 4 aliquot portions were mixed and ground with chloroform to remove non-quaternary bases. The chloroform-soluble portion was mixed with the main chloroform extracts containing the non-quaternary bases and, on removal of solvent, gave 12·8 g. of non-quaternary bases which on titration required 30·5 c.c. of N-hydrochloric acid for neutralisation. This solution was extracted with chloroform to remove fat (0·3 g.) and then the alkaloids were liberated fractionally in the presence of chloroform by addition of 14 successive portions (each 2·5 c.c.) of N-sodium carbonate solution. Each of the 14 chloroform extracts was evaporated to dryness and moistened with methyl alcohol. Fractions 5 to 9 readily crystallised, the solid in each case proving to be *lævo*bebeerine, m. p. 212° not depressed by admixture with authentic *lævo*bebeerine and raised to 287° by admixture with *dextro*bebeerine, total yield 2·24 g. Fraction 8 on keeping deposited *dextro*chondrocurine, m. p. 236°, and fraction 9 later deposited *iso*chondrodendrine (0·12 g., m. p. 309°) and still later *dextro*chondrocurine (0·25 g., m. p. 240°). Fractions 10 to 12 gave *iso*chondrodendrine (1·02 g., m. p. 305°).

The methyl alcoholic mother liquors of fractions 3 to 9 were then mixed, the solvent removed, and the alkaloidal residue titrated with N-hydrochloric acid (7·5 c.c.) and again fractionally liberated into chloroform by the successive addition of 13 portions, each of 0·75 c.c. of N-sodium carbonate solution. On removal of the chloroform from each, the residue was moistened with methyl alcohol as before and all fractions crystallised with the exception of the first. Fractions 3 to 5 gave *lævo*bebeerine (0·3 g.), fractions 6 to 8 gave crude *dextro*chondrocurine (0·37 g.), whilst fractions 10 to 13 gave *iso*chondrodendrine (90 mg.). Fraction 2 contained a readily-soluble alkaloid crystallising in clear tablets, m. p. 274°. It gave no Millon reaction, was non-phenolic, and was stable to warm dilute nitric acid. These properties agree very well with those recorded by Dutcher (*loc. cit.*) and Kondo, Tomita, and Uyeo (*Ber.*, 1937, **70**, 1890) for *dextroiso*chondrodendrine dimethyl ether.

The combined crops of *lævo*bebeerine (2·55 g.) were converted into the hydrochloride (2·42 g., m. p. 275° efferv.). In a similar way the combined crops of *iso*chondrodendrine (1·23 g.) were neutralised with sulphuric acid and gave the very characteristic octahedra of *iso*chondrodendrine sulphate (1·21 g., m. p. 290° efferv.). The combined fractions of *dextro*chondrocurine (0·64 g.) were converted into the *hydrochloride*, m. p. 288° (efferv.), yield 0·41 g. This salt crystallised in elongated hexagonal plates which at first contained 6·5 molecules of water of crystallisation, but after a few days this had fallen to 2·5

molecules (Found, on fresh air-dried salt: loss at 110°, 14·5. $C_{36}H_{38}O_6N_2,2HCl,6{\cdot}5H_2O$ requires H_2O 14·9%. On further air-drying: loss at 100°, 6·5. $C_{36}H_{38}O_6N_2,2HCl,2{\cdot}5H_2O$ requires H_2O, 6·3%. On solid dried at 100°: C, 64·3; H, 6·3; MeO, 8·9. $C_{36}H_{38}O_6N_2,2HCl$ requires C, 64·7; H, 6·0; 2MeO, 9·3%). The rotation of the salt was determined in water, $[\alpha]_D^{20°}$ +208·7°, for the anhydrous salt (*c*, 0·57), whence $[\alpha]_D^{20°}$ +233° for the ion. Dutcher (*loc. cit.*) gives $[\alpha]_D^{24°}$ +193° for anhydrous *dextro*chondrocurine sulphate whence $[\alpha]_D^{24°}$ +224° for the ion. The base was recovered from the hydrochloride and crystallised from methyl alcohol, yield 0·24 g., m. p. 236—238° (Found: MeO, 10·4, 10·8. Calc. for $C_{36}H_{38}O_6N_2$: 2MeO, 10·4%). Dutcher (*loc. cit.*) gives m. p. of the base 232—234°.

The above mentioned sodium hydrogen carbonate precipitate (9·5 g.) which had been extracted with chloroform to remove all soluble bases was treated with N-hydrochloric acid (60 c.c.) and a tarry fraction removed. It was precipitated with ammonium reineckate and the precipitate converted into the chloride. Ammonia was added to remove chromium as hydroxide and the solution on concentration eventually deposited a further quantity (0·49 g.) of of *dextro*tubocurarine chloride.

Chondrodendron tomentosum *Stems from Tarapoto, Peru.—Chondrodendron tomentosum* stems (1·08 kg.) were received from Mr. H. W. Massey. They were collected at Sisa near Tarapoto and leaves were obtained at the same time and were identified by Mr. N. Y. Sandwith, M.A., as being indistinguishable from *Ch. tomentosum* leaves.

The stems were powdered, extracted with 15 litres of 1% tartaric acid, and the extract concentrated to 3·6 litres. Of this solution a portion (250 c.c.) was treated with basic lead acetate solution (100 c.c., 0·5N) and the filtrate freed from lead by passing hydrogen sulphide. The filtrate (500 c.c.) freed from lead sulphide and excess of hydrogen sulphide required 25 g. of sodium hydrogen carbonate to make the solution alkaline. After standing for a few days the solid A (1·93 g.) was removed and the aqueous solution extracted repeatedly with chloroform which removed 0·18 g. (B) of non-quaternary alkaloid. The extracted aqueous solution was made weakly acid with concentrated hydrochloric acid (27·5 c.c.) and treated with saturated ammonium reineckate solution (100 c.c.). The precipitated reineckate was converted into chloride and the solution on concentration gave 0·37 g. of crystalline *dextro*tubocurarine chloride; $[\alpha]_D^{20°}$ +202° (*c*, 0·53), for the anhydrous salt. A small second crop (0·1 g.) was obtained from the mother liquor.

The solid A (1·93 g.) was treated with chloroform which removed 0·92 g. of non-quaternary bases which were mixed with fraction B (0·18 g.) and dissolved in methyl alcohol. On keeping, crystalline microscopic spheroids of *dextroiso*chondrodendrine separated (80 mg.), m. p. 306°. It gave the very characteristic sulphate crystallising in glassy octahedra, and the dextro-rotation was confirmed by neutralising the base (80 mg.) with N/10-sulphuric acid, when $[\alpha]_D^{17°}$ was +140·6° calculated in terms of the base.

The chloroform-insoluble solid (1·01 g.) was neutralised with N-hydrochloric acid (5·0 c.c.), treated with saturated ammonium reineckate solution (40 c.c.) and the solid collected and converted into chloride. The solution on concentration deposited *dextro*tubocurarine chloride (0·32 g.), $[\alpha]_D^{21°}$ +195·5° (*c*, 0·4), for the anhydrous salt.

Isolation of lævo*Bebeerine*, dextro*Chondrocurine*, dextroiso*Chondrodendrine, and Tomentocurine from the Non-quaternary Bases.*—The remainder (3350 c.c.) of the original tartaric acid extract was cleaned up with basic lead acetate and concentrated to 2000 c.c. This was made alkaline by addition of sodium hydrogen carbonate and the precipitated solid A removed after keeping for 24 hours. The filtrate was repeatedly extracted with chloroform which removed the remainder (2·0 g.) of the non-quaternary bases. The precipitated solid A, was dried in a vacuum and extracted with chloroform which removed 14·0 g. of non-quaternary bases. The combined crops of non-quaternary bases were neutralised with N-hydrochloric acid (42 c.c.) and then divided into 16 chloroform-soluble fractions by first extracting with chloroform to remove fat and then with chloroform after addition of 15 portions, each of 3 c.c., of N-sodium carbonate solution. The average weight of base in each chloroform-soluble fraction was about a gram. The 15 basic fractions were each dissolved in methyl alcohol (3—4 c.c.) and kept. Fractions 3 to 5 deposited *lævo*bebeerine (1·45 g.), m. p. 212°, undepressed by an authentic sample, and giving the hydrochloride (0·97 g.), m. p. 278° (efferv.), $[\alpha]_{5461}^{20°}$ −259° (*c*, 0·52) for the anhydrous salt. Fractions 8 to 13 gave *dextroiso*chondrodendrine (1·66 g.), m. p. 306—310°. It was converted into the sulphate (1·69 g.), m. p. 292° (decomp.), and gave $[\alpha]_D^{20°}$ +113·6°; $[\alpha]_{5461}^{20°}$ +145·7° for the anhydrous salt. On more prolonged keeping, fractions 6 to 10 all deposited *dextro*chondrocurine (1·45 g. in all), m. p. 237—238°, which was converted into the hydrochloride (1·35 g.), m. p. 285—286°. It lost 7·7% on drying, corresponding to 3 molecules of water of crystallisation, and had $[\alpha]_{5461}^{20°}$ +247°; $[\alpha]_D^{20°}$ +210° for the anhydrous salt (*c*, 0·46). This agrees with the value $[\alpha]_D^{20°}$ +208·7° found for *dextro*chondrocurine hydrochloride isolated from commercial curare (described above).

On more protracted keeping fractions 6 to 8 gave *lævo*bebeerine (0·94 g.). A special search was made for *iso*chondrodendrine dimethyl ether by combining the mother liquors of fractions 1 to 7 by evaporating to dryness and solution of the residue in chloroform. Phenolic alkaloids were removed by N-sodium hydroxide and on liberation to chloroform by passage of carbon dioxide gave a phenolic fraction of 3·2 g. The non-phenolic fraction left in the chloroform after alkaline extraction amounted to 0·29 g. but all attempts to crystallise *iso*chondrodendrine dimethyl ether from it failed. The phenolic fraction was again separated into 12 fractions of different basicity and gave *lævo*bebeerine (0·17 g.), *dextro*chondrocurine (0·59 g.), and *dextroiso*chondrodendrine (0·14 g.). Fractions 11 and 12, representing the most basic fractions, gave 75 mg. of a new alkaloid, m. p. 260—270°.

As this new base appeared at the end of the *iso*chondrodendrine fractions it was of interest to examine the mother liquors of fractions 8 to 13 of the original scheme of fractionation. The combined alkaloidal bases from the evaporated methyl alcoholic solutions were neutralised with acid and fractionally liberated to chloroform in 10 fractions from which *dextro*chondrocurine (0·18 g.) and *dextroiso*chondrodendrine (0·11 g.) were obtained and finally from the most basic fraction 10, a further 60 mg. of the new alkaloidal base, m. p. 265°.

The three fractions (135 mg. in all) of the new alkaloidal base for which the name *tomentocurine* is proposed were combined and neutralised with N/10-sulphuric acid (2·7 c.c.) and the solution evaporated. The characteristic octahedra of *dextroiso*chondrodendrine did not separate. The base was regenerated

to chloroform, the solvent evaporated to a small volume, and then methyl alcohol (5 c.c.) added. There was instantaneous crystallisation of tomentocurine base as a microcrystalline powder (70 mg.) similar in appearance to *iso*chondrodendrine but with m. p. 265° (efferv.). It gave a Millon reaction and was readily oxidised by dilute nitric acid thus resembling all the phenolic alkaloids of this group. On drying at 100° it lost 7% and the dried solid in N/10-hydrochloric acid had $[\alpha]_D^{17°}$ +210°; $[\alpha]_{5461}^{17°}$ +278·5° in terms of the base (*c*, 0·15). These rotations are far higher than those of *dextroiso*chondrodendrine. The hydrochloric acid solution was evaporated to a syrup but the hydrochloride could not be induced to crystallise.

The composition of the base (Found: C, 69·6; H, 8·2; N, 3·5, 3·9; OMe, 21·3%) was difficult to reconcile with a member of this group of alkaloids. Owing to the very small amounts of material available confirmation of the analytical figures has not been possible and they are not regarded as final.

From the main liquor containing quaternary bases, *dextro*tubocurarine chloride (3·8 g.) was isolated through the reineckate. The sodium hydrogen carbonate precipitate (A) from which chloroform-soluble alkaloids had been removed was neutralised with N-hydrochloric acid (85 c.c.) and treated with saturated ammonium reineckate solution (650 c.c.). The precipitated reineckate was converted into chloride and material precipitable by dilute ammonia removed in dilute solution. On concentration and inoculation the solution slowly deposited *dextro*tubocurarine chloride (1·6 g.) but not with the ease of the preliminary run on 250 c.c. of original stem extract.

The Rotation of dextroiso*Chondrodendrine.*—For two commercial samples of *iso*chondrodendrine sulphate Faltis and Neumann (*Monatsh.*, 1921, **42**, 321) give $[\alpha]_D^{21°}$ +135° and $[\alpha]_D^{16°}$ +114·7° for the anhydrous salt. In Part V (King, *J.*, 1940, 745) a value $[\alpha]_{5461}$ +115·6° was recorded for the anhydrous sulphate which corresponds to a value $[\alpha]_D$ +99·7° if Biot's law holds. Dutcher (*J. Amer. Chem. Soc.*, 1946, **68**, 423) gives a value $[\alpha]_D^{22°}$ +101° for the anhydrous salt. Earlier in this communication $[\alpha]_D^{20°}$ +113·6° and $[\alpha]_{5461}^{20°}$ +145·7° were recorded for anhydrous *iso*chondrodendrine sulphate which had been prepared from specimens of *iso*chondrodendrine obtained by a fractionation depending on different basicities. As this value was considerably higher than the figure given in Part V and the figure given by Dutcher, a sample of *dextroiso*chondrodendrine sulphate was recrystallised several times from water and gave $[\alpha]_{5461}^{19°}$ +158·9° (*c*, 0·7) for the anhydrous salt, whence $[\alpha]_D^{19°}$ +137° if Biot's law holds. This is a value very close to that given for a sample of the commercial sulphate by Faltis and Neumann.

Examination of Anomospermum grandifolium, *Eichl.*—The stems (484 g.) were extracted with 1% tartaric acid until the alkaloids were removed and the solution concentrated to 400 c.c. When tested by Dr. F. C. MacIntosh it was found, by the rabbit head-drop test, to have a curare action corresponding to that of a 0·01% solution of *dextro*tubocurarine chloride.

The alkaloids were then separated into chloroform-soluble non-quaternary bases and quaternary bases (precipitated by ammonium reineckate). The total chloroform-soluble bases amounted to 0·2 g. with a weak curare action when made up to 20 c.c. in neutral solution equivalent to a 0·006% solution of *dextro*tubocurarine chloride.

The quaternary fraction as chloride was made up to 10 c.c. and had an effect on the rabbit indistinguishable from that of a 0·2% solution of *dextro*tubocurarine chloride.

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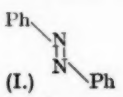
395. *The Dipole Moments of Benzocinnoline and Benzocinnoline Oxide in Relation to those of* cis-*Azo- and -Azoxy-benzene.*

By K. E. CALDERBANK and R. J. W. LE FÈVRE.

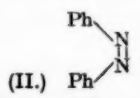
The identifications of the azo- and azoxy-benzenes of m. p.s 71° and 84° as the *cis*-isomers, made previously on dipole-moment evidence, receive further support from an examination of benzocinnoline and its *N*-oxide.

HARTLEY and LE FÈVRE (*J.*, 1939, 531) discussed the dipole moments found for the two isomeric azobenzenes (I, II) in reference to *inter alia* those previously recorded (Gehrckens and Müller, *Annalen*, 1933, **500**, 296) for the (apparently) corresponding azoxybenzenes (III, IV). Circumstances then prevented the intended extension of the argument by analogy to benzocinnoline (V) and its *N*-oxide (VI).



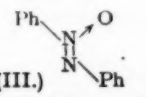
(I.)

M. p. = 68°, μ = *ca.* 0 D.



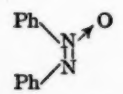
(II.)

M. p. = 71°, μ = 3·0 D.



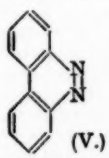
(III.)

M. p. = 36°, μ = 1·7 D.



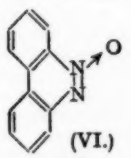
(IV.)

M. p. = 84°, μ = 4·7 D.



(V.)

μ = 3·9 D.



(VI.)

μ = 5·2 D.

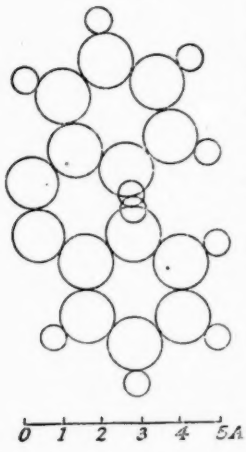
These two compounds are now found to have the moments shown above. In both cases the values are higher than those of the related diaryl *cis*-substances (II) and (IV), but not more so than might be expected from other pairs, such as :

	μ, D.			μ, D.	
Diphenylamine [1]	1·0	(A)	Diphenyl ether	0·9	(B)
Carbazole [2]	2·09		Diphenylene oxide	1·2	
Benzoic anhydride [3]	4·15	(C)	Diphenylmethane	0·23	(D)
Diphenic anhydride [4]	5·3		Fluorene [5,6]	0·5—0·8	
Benzophenone	3·0	(E)	*cis*-Stilbene	0	(F)
Fluorenone [5]	3·35		Phenanthrene	0·6	
			Benzil [7]	3·7	(G)
			Phenanthraquinone [7]	5·6	

[1] Smythe, unpublished determination. [2] Cowley and Partington, *J.*, 1936, 47. [3] Oesper and Smyth, *J. Amer. Chem. Soc.*, 1942, **64**, 768. [4] Le Fèvre and Vine, *J.*, 1938, 972. [5] Hughes, Le Fèvre, and Le Fèvre, *J.*, 1937, 202. [6] Sirkin and Schott-Lvova, *Acta Physicochim. U.R.S.S.*, 1944, **19**, 379. [7] Caldwell and Le Fèvre, *J.*, 1939, 1614.
Other figures (unmarked) from *Trans. Faraday Soc.*, 1934, **30**, Appendix.

It is clear that several causes may operate to produce the increases of moment noted, *e.g.*, geometrical distortion due to ring closure, prevention of rotation of the phenyl groups in all cases, and of the benzoyl groups in (C) and (G), with consequent alteration of the anisotropy of molecular polarisability, and hence the degree of internal induction of polarisation by the stronger dipolar links present, change of bond moments by *oo'*-covalent union [*e.g.*, μ_{CO} or μ_{HC} in (C) and (E)], or what amounts to the same thing—modification of mesomeric forms following the increased possibilities of conjugation, etc.

FIG. 1.



These phenomena, in general, are difficult to diagnose separately. However, for certain instances—such as (II) and (V), (IV) and (VI), (A) and (B)—where the resultant is largely the vector sum of two Ar→X components, rough estimation of the part played by the geometrical explanation seems straightforward. As an illustration we consider the molecules (II) and (V).

Fig. 1 is a scale drawing, flattened into the plane of the paper, of *cis*-azobenzene, based on the *X*-ray analyses by Robertson (*J.*, 1939, 232; Hampson and Robertson, *J.*, 1941, **63**, 2533). Inspection suggests that this, and many similar diaryl compounds, in assuming such a configuration would need to adopt an *oo'*-carbon-to-carbon separation of 1·78 A.; *i.e.*, less than the C . . . C total "Wirkungs-radien" (about 3—3·5 A.; Stuart, *Z. physikal. Chem.*, 1935, *B*, **27**, 353). For the stable state of these molecules, a degree of rotation (Robertson finds 50°) of the Ar-nuclei around their 1 : 4-axes is therefore understandable. Covalent union between the appropriate *ortho*-carbon atoms will, however, require an interatomic distance less than 1·78 A., namely, about 1·49 A. (the 1 : 1'-C–C distance in diphenyl). Now, the observed moment of *cis*-azobenzene is very largely a resultant of the two C→N moments, interacting at approximately 70°. A reduction of the 2 : 2'-C–C distance by 0·29 A. will tend to reduce this angle, and provided the magnitudes of the principle vectors and inter-atomic distances other than the 2 : 2'- are unaltered, to *raise* the molecular resultant moment. However, calculation shows that, from this cause, the moment of (V) should only be 103·3% of that of (II). In *fact* it is 130%, and we conclude therefore that polarisability and mesomeric, rather than geometric, factors are predominantly responsible for the point under discussion.

EXPERIMENTAL.

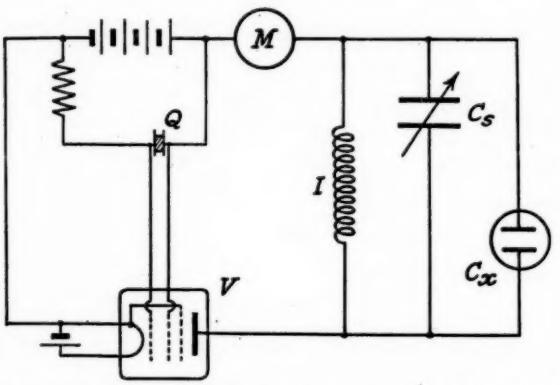
Apparatus.—The earlier measurements (*loc. cit.*) on *cis*- and *trans*-azobenzene were made on the resonance apparatus described by Le Fèvre and Russell (*Trans. Faraday Soc.*, 1947, **43**, 374). In Sydney, however, we have adopted, with satisfactory results, a further slight simplification (Fig. 2) of the elementary circuit arrangement mentioned in "Dipole Moments" (2nd Edition, Methuen, London, 1948, pp. 33 and 34). The chief modifications are that the valve, *V* (Radiotron 1F4, but others such as the Radiotron 33 or Osram KT2 or KT24 have been found to work equally well), the mounted quartz crystal section, *Q* (Frequency 1 mc.), the 0—10 milliammeter, *M*, and the coil, *I* (interchangeable plug-in type, for easy accommodation in C_x of liquids of different dielectric constants), are built on a 6″ × 5″ × 3″ ordinary radio chassis. At one end, battery connections are made by a multi-pin telephone plug, while from the other, shielded coaxial cables run in parallel to a Sayce–Briscoe cell, C_x (in an earthed thermostat),

and to a standard variable Sullivan condenser, C_s (fitted with a slow-motion worm-drive which also serves as a revolution counting head). All other essential features remain as previously described (cf. *op. cit.*, Chapter II).

Materials.—*trans*-Azoxybenzene and benzocinnoline and its oxide were recrystallised from ethanol, and eventually had m. p.s 38—38·5°, 153—154°, and 139—139·5°, respectively. The literature values are 36° (Zinin, *J. pr. Chem.*, 1845, **36**, 99); 156° (Täuber, *Ber.*, 1891, **24**, 3085); 139° (Ullmann and Dieterle, *Ber.*, 1904, **37**, 24) or 152° (Täuber, *loc. cit.*), respectively. The 36° m. p. of azoxybenzene appears to have remained unquestioned for a century (see Beilstein, "Handbuch", XVI, 621; XVI*, 376). Our specimen formed nearly colourless needles, in contrast with the "hellgelbe Nadeln" or the "farbloser Plättchen" (Knipscheer, *Rec. Trav. chim.*, 1903, **22**, 21) of the literature. We have therefore repeated the U.V. absorption spectrum and the dipole-moment determination recorded for this substance by Müller (*Annalen*, 1932, **493**, 166; Gehrckens and Müller, *loc. cit.*).

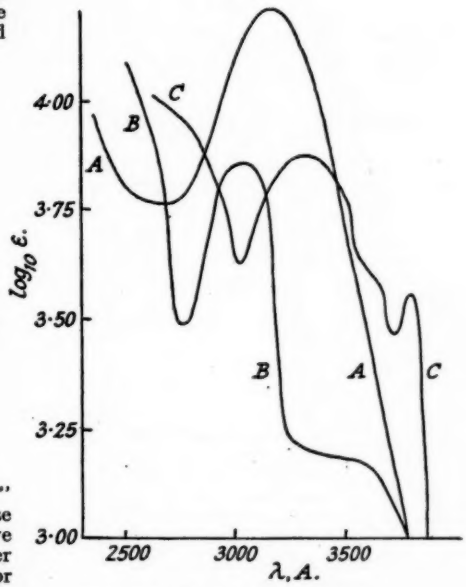
Absorption Spectra.—Since the U.V. spectra of most substituted azobenzenes (Cook, Jones, and Polya, *J.*, 1939, 1315) are characterised by two bands in the regions 3000—3600 A. ("*K*" bands, $\log_{10}\epsilon$ usually *ca.* 4) and 4400—4500 A. ("R" bands, $\log_{10}\epsilon$ usually between 2 and 3), and because the former are ascribed (*idem, ibid.*) to general conjugation between the -N=N- system and the Ar nuclei, it seemed possible that information relevant to the point raised above would

FIG. 2.



be revealed by ascertaining the positions of the "*K*" bands in benzocinnoline and its oxide relatively to those in *cis*-azo- and -azoxy-benzene. Absorption spectra have been accordingly determined in ethyl alcohol, a Hilger medium spectrograph being used with a rotating sector photometer and condensed tungsten-steel spark (see Fig. 3). The appropriate comparisons can be readily made from the following table (which includes certain earlier observations):

FIG. 3.



Curve A: trans-*Azoxybenzene*.
Curve B: *Benzocinnoline*.
Curve C: *Benzocinnoline oxide*.

Compound.	Solvent.	$\lambda_{max.}$	$\log_{10}\epsilon$.	Ref.
Benzocinnoline	EtOH	3000	3·87	Present work
cis-Azobenzene	C_6H_6	*ca.* 3000	*ca.* 3·6	Le Fèvre and Vine (*J.*, 1938, 431)
,,	$CHCl_3$	3240	4·18	Cook, Jones, and Polya (*loc. cit.*)
,,	EtOH	3050	3·4—3·5	Winkel and Siebert (*Ber.*, 1941, **74**, 675)
Benzocinnoline oxide	EtOH	3320	3·86	Present work
cis-Azoxybenzene	EtOH	3350	(3·8—3·9) *	Müller (*loc. cit.*)
trans-Azobenzene	C_6H_6	3300	4·3	Le Fèvre and Vine (*loc. cit.*)
,,	$CHCl_3$	3190	4·29	Cook, Jones, and Polya (*loc. cit.*)
,,	EtOH	3200	4·2	Winkel and Siebert (*loc. cit.*)
trans-Azoxybenzene	EtOH	3200	4·22 *	Present work
,,	,,	3250	(not given)	Müller (*loc. cit.*)

* Müller does not record $\log_{10}\epsilon$ for either *cis*- or *trans*-azoxybenzene but states that the intensity of absorption of the first is approximately half that of the second. Since we find $\log_{10}\epsilon$ for the *trans*-form to be 4·22 we therefore quote 3·8—3·9 for the *cis*-isomer.

The covalent union of the *oo'*-atoms of *cis*-azobenzene is not therefore accompanied by the increases in wave-length and intensity of absorption to be expected if benzocinnoline is the more "conjugated" of the two molecules. *cis*-Azoxybenzene and benzocinnoline oxide similarly show practically no differences.

Incidentally, the above results do not confirm the statement that the absorption of azobenzene is nearly the same as liquid or vapour or solute in polar and non-polar solvents (Horio and Yamashita, *J. Soc. Chem. Ind. Japan*, 1934, **37**, 491; Uémura and Inamura, *Bull. Chem. Soc. Japan*, 1935, **10**, 169).

Dielectric-polarisation Measurements.—These are set out under the customary headings (explained in *J.*, 1937, 1805). The solvent was " A.R." grade benzene purified by partial freezing, decantation, and drying over sodium wire, etc. (cf. *op. cit.*, p. 31).

100 w_1.	$\epsilon_{27°}$.	$d_4^{27°}$.	$\alpha\epsilon_2$.	βd_2.	100 w_1.	$\epsilon_{27°}$.	$d_4^{27°}$.	$\alpha\epsilon_2$.	βd_2.
0	2·2685	0·86934	—	—	0	2·2685	0·86934	—	—
				trans-*Azoxybenzene.*					
0·5036	2·2774	0·87041	1·75	0·212	2·0211	2·3032	0·87369	1·72	0·215
0·8678	2·2835	0·87129	1·72	0·225	2·6607	2·3212	0·87543	1·98	0·229
1·0830	2·2863	0·87177	1·64	0·224					
				Benzocinnoline.					
0·1656	2·2841	0·86976	9·34	0·278	0·7596	2·3493	0·87139	10·63	0·275
0·3645	2·3078	0·87033	10·77	0·283	1·1048	2·3831	0·87225	10·38	0·267
				Benzocinnoline oxide.					
0·2350	2·3034	0·87007	14·9	0·328	0·5608	2·3576	0·87113	15·9	0·326
0·3508	2·3255	0·87045	16·3	0·328	0·6526	2·3715	0·87137	15·8	0·317
0·4315	2·3356	0·87067	15·6	0·318	0·7348	2·3866	0·87163	16·1	0·317

Refractivities.—These have been measured (Abbé refractometer) in chlorobenzene :—

100 w_1.	$n_D^{25°}$.	$d_4^{25°}$.	r_{12}, c.c.	r_1, c.c.	$[R_L]_D$, c.c.
0	1·5251	1·1015	0·2783	—	—
			trans-*Azoxybenzene.*		
4·6460	1·5331	1·1052	0·2809	0·3343	66·2
			Benzocinnoline.		
6·6640	1·5371	1·1081	0·2819	0·3323	65·1
			Benzocinnoline oxide.		
4·0946	1·5336	1·1063	0·2808	0·3394	66·2

Von Auwers (*Annalen*, 1932, **499**, 131), from observations on quinoline solutions, reported $[R_L]_D = 63·6$ and 61·2 c.c., respectively, for azoxybenzene and its " iso- "form.

Dipole Moments.—The requisite mean values from the above data are used in conjunction with the appropriate constants, namely, $p_2 = 0·34184$; $C = 0·18941$ (cf. *J.*, 1937, 1805) :

	Mean $\alpha\epsilon_2$.	Mean β.	P_T, c.c.	$[R_L]_D$.	μ, D.
trans-Azoxybenzene	1·76	0·252	116·6	66·2	1·57
Benzocinnoline	10·28	0·317	382·3	65·1	3·93
Benzocinnoline oxide.....	15·77	0·371	627·6	66·2	5·22

The moment now recorded for azoxybenzene is slightly lower than that given by Gehrckens and Müller (*loc. cit.*), who, however, were working at an unstated temperature.

The standard condenser used was originally provided by a Research Grant from this Society; for its continued possession and permission to bring it to Australia, the authors record grateful acknowledgment.

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396. *The Action of Nitrosyl Chloride on Some Metals and Their Compounds.*

By J. R. PARTINGTON and A. L. WHYNES.

The action of nitrosyl chloride on several metals and their chlorides has been reinvestigated and much of the earlier work confirmed. The reaction has been extended to thallium, and a new method for the preparation of Tl_2Cl_3 described. Two new *compounds*, $InCl_3$,NOCl and $GaCl_3$,NOCl, have been prepared in several ways.

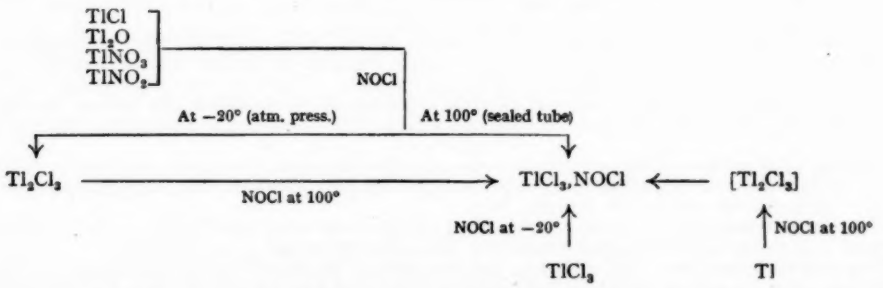
WEBER (*Ann. Phys. Chem.*, 1863, **118**, 471) found that stannic chloride and titanium tetrachloride absorb " the very carefully dried vapour set free from concentrated aqua regia on warming," and that ferric chloride and aluminium chloride melt when heated in a gentle stream

of the vapour. His descriptions of the reactions are concise and accurate, and he recognised that the product was a compound of the metal chloride and nitrosyl chloride.

Geuther (*J. pr. Chem.*, 1874, **8**, 354) prepared BCl_3,NOCl by the action of dinitrogen tetroxide on boron trichloride and sublimation of the product. Sudborough (*J.*, 1891, **59**, 655) obtained the following compounds: $ZnCl_2$,NOCl, TlCl,$TlCl_3$,2NOCl, $FeCl_3$,NOCl, $SnCl_4$,2NOCl, $(SbCl_5)_2$,5NOCl, $BiCl_3$,NOCl, $AuCl_3$,NOCl, and $PtCl_4$,2NOCl. Although lead, mercury, aluminium, manganese, nickel, and arsenic formed the corresponding metallic chlorides, no stable addition products were observed. Cuttica, Tarchi, and Alinari (*Gazzetta*, 1923, **53**, 189) prepared CuCl,NOCl, and $TlCl_2$,3NOCl by the action of nitrosyl chloride in a sealed tube on cuprous oxide and thallous oxide. The compound $TlCl_2$,3NOCl has been wrongly reported in the literature as "thallous nitrosyl chloride," 2TlCl,3NOCl (Mellor, "Treatise, etc.," 1928, **8**, 617), and as $TlCl_2$,NOCl (*Chem. Zentr.*, 1923, III, 357). Gall and Mengdehl (*Ber.*, 1927, **60**, 86) and Rheinbold and Wasserfuhr (*ibid.*, p. 732) prepared $AlCl_3$,NOCl from aluminium chloride, whilst Sudborough obtained only aluminium chloride from aluminium and nitrosyl chloride. Asmussen (*Z. anorg. Chem.*, 1939, **243**, 127) measured the magnetic susceptibilities of some of the addition compounds and analysed most of them, including $AlCl_3$,NOCl and TlCl,$TlCl_3$,2NOCl.

Thallium sesquichloride, 3TlCl,$TlCl_3$ or Tl_2Cl_3, was first prepared by Crookes and Church (*Chem. News*, 1863, **8**, 1) by evaporation of a solution of thallous chloride with aqua regia until the evolution of chlorine ceased, but analyses by Werther (*J. pr. Chem.*, 1864, **91**, 385) gave the ratio Tl : Cl varying from 2 : 3 to nearly 1 : 3. Thomas (*Compt. rend.*, 1906, **142**, 840) stated that excess of liquid chlorine converts thallous chloride completely into Tl_2Cl_3, but he later (*Ann. Chim. Phys.*, 1907, **11**, 204) found that very dry liquid chlorine does not attack thallous chloride, and was unable to specify conditions for the exclusive formation of Tl_2Cl_3. Gogorishvili and Kul'gini (*J. Gen. Chem. Russia*, 1938, **8**, 302) prepared Tl_2Cl_3 by passing a current of chlorine into a solution containing a mixture of thallous sulphate and thallous nitrate with 30% hydrogen peroxide at room temperature.

The discrepant results with the aluminium and thallium compounds were thought worthy of reinvestigation. It was found that aluminium metal and aluminium trichloride gave the same product, $AlCl_3$,NOCl, with nitrosyl chloride. The products with thallous compounds and nitrosyl chloride varied with temperature. Thallium sesquichloride was obtained in theoretical yield by the action of nitrosyl chloride on thallous chloride at −20° and atmospheric pressure, and this reaction gives a convenient method of preparation: $2TlCl + NOCl = Tl_2Cl_3 + NO$. With thallous oxide the reaction is $Tl_2O + 3NOCl = Tl_2Cl_3 + 2NO + NO_2$. (Dinitrogen tetroxide has no action on thallium sesquichloride.) Thallous nitrate and nitrite were first converted into chloride, which then reacted as above with excess of nitrosyl chloride: $TlNO_3 + NOCl = TlCl + NO{\cdot}NO_3$ (*i.e.*, N_2O_4), and $2TlNO_2 + 3NOCl = Tl_2Cl_3 + 2N_2O_3 + NO$. The product obtained from thallium and nitrosyl chloride at 100° was $TlCl_3$,NOCl, chlorination taking place in stages; some Tl_2Cl_3 was isolated in the reaction. Thallous oxide and nitrosyl chloride at 100° gave $TlCl_3$,NOCl, which was also formed from thallous chloride, nitrate, nitrite, or the sesquichloride, and nitrosyl chloride in a sealed tube at 100°. Thallous bromide and thallous iodide and nitrosyl chloride formed $TlCl_3$,NOCl with liberation of bromine and iodine. At −20° nitrosyl chloride reacted directly with anhydrous thallic chloride forming $TlCl_3$,NOCl. Reactions between thallous compounds and NOCl are summarised below.



Indium metal, indium monochloride, dichloride, and trichloride all gave a new *compound* $InCl_3$,NOCl. The chlorine of nitrosyl chloride replaces bromine in indium mono- or tri-bromide to give the trichloride, a molecule of nitrosyl chloride then being added to give the same compound. Indium dichloride or trichloride is most suitable for the preparation of $InCl_3$,NOCl.

Gallium reacts vigorously with nitrosyl chloride to form the new *compound* $GaCl_3,NOCl$, which is also obtained from gallium trichloride.

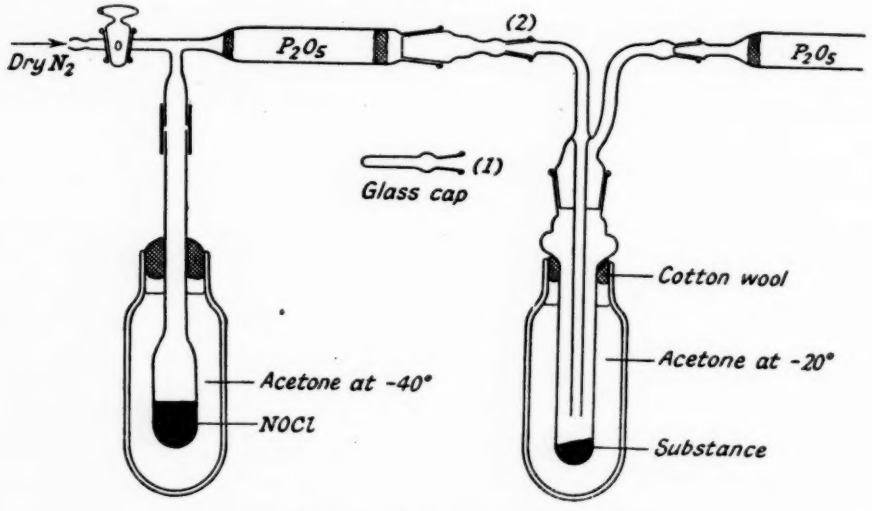
Experimental.

Preparation of Nitrosyl Chloride.—Nitrosyl chloride was obtained by warming nitrososulphuric acid and sodium chloride below 100° (Tilden, *J.*, 1874, **27**, 630). An all-glass apparatus was used, the gas being thoroughly dried with phosphoric oxide, condensed at −20°, and fractionally distilled in a slow current of nitrogen. The receivers were " Pyrex " tubes 14 cm. long, of 55 ml. capacity, and having 20-cm. necks. A small portion evaporated completely before the ice round the trap had melted, which was not the case if any nitrogen dioxide was present. Nitric oxide forms an almost black solution with nitrosyl chloride, and this accounts for the colour change in some reactions.

Two methods were used for reaction of nitrosyl chloride with metals and metallic salts: (*a*) the nitrosyl chloride was kept in contact with the substance at a low temperature (*e.g.*, −20°) for some hours; (*b*) nitrosyl chloride was sealed with the substance, then heated to 100°. These methods are described in detail.

(*a*) The tube of nitrosyl chloride was cooled to −40° in a narrow-mouthed Dewar flask, and the tip broken, a piece of pressure tubing fitted, and the phial connected to the apparatus. Rubber is only slowly attacked by nitrosyl chloride. Dry nitrogen was passed through for some time, the Dewar flask removed, and the required amount of nitrosyl chloride allowed to distil, dried through 20 cm. of phosphoric oxide, and condensed in a trap on the substance, the exit tube being protected by 20 cm. of

Fig. 1.



phosphoric oxide. By varying the amount of solid carbon dioxide added, any temperature between 10° and −70° could be obtained. Excess of nitrosyl chloride was distilled off by putting a small glass cap (1) (see Fig. 1) on the ground glass joint (2), removing the cooling bath from the trap, and allowing it to warm to room temperature. (*b*) The vapour pressure of nitrosyl chloride is considerable at 100°. Ordinary " Pyrex " tube, 1½ cm. diameter with 1-mm. walls, bursts at this temperature. The sealed tubes used were 1—1·5 cm. diameter with 3-mm. walls.

After reaction, the tube was cooled in solid carbon dioxide, whereupon the nitrosyl chloride solidified, but there was a considerable pressure of nitric oxide. The tip of the tube was heated with an oxygen flame, and a small hole 2 mm. in diameter blown in the glass. This was enlarged, the tube connected to the receiver, and the excess of nitrosyl chloride distilled off by removing the carbon dioxide jacket. The solid was quickly brought from the tube into a desiccator over concentrated sulphuric acid for about 5 minutes.

Methods of Analysis.—The compounds were very deliquescent; they were weighed in tightly stoppered bottles or in very thin glass bulbs which were broken by vigorous shaking with water in a stoppered bottle. The solution was always strongly acid.

Chlorine determination. Silver chloride was precipitated after acidification with nitric acid and weighed. A special method is described under the particular metal (*e.g.*, thallium).

Nitrogen determination. The nitrogen was determined by dissolving the substance in 5% sodium hydroxide solution, adding 10 ml. of 20% sodium hydroxide and 3 g. of very fine Devarda's alloy, and after 1 hour distilling the ammonia into standard hydrochloric acid, the excess being titrated with 0·1N-sodium hydroxide and methyl-red.

Formulæ of compounds previously described were confirmed by the following results. (S, Sudborough; C, Cuttica *et al.*; A, Asmussen; G.M., Gall and Mengdehl; W, Weber; R.W., Rheinbold and Wasserfuhr; *locc. cit.*)

Starting material.	Product.	Reference.	Found, %.			Required, %.		
			Cu.	Cl.	N.	Cu.	Cl.	N.
Cu	CuCl,NOCl	S.	39·19	43·45	8·01	38·64	43·14	8·5
Cu_2O	CuCl,NOCl	C.	38·02	42·82	—	—	—	—
CuCl	CuCl,NOCl	C., A., G.M.	38·16	43·62	—	—	—	—
			Zn.	Cl.	N.	Zn.	Cl.	N.
Zn	$ZnCl_2$,NOCl	S., A.	32·03	53·3	6·1	32·4	52·74	6·9
			Hg.	Cl.	N.	Hg.	Cl.	N.
$HgCl_2$	$HgCl_2$,NOCl	G.M., A.	60·14	31·16	4·40	59·5	31·58	4·15
HgCl	$HgCl_2$,NOCl	G.M.	Cl/Hg = 2·96		—	Cl/Hg = 3·0		
			Ti.			Ti.		
$TiCl_4$	$TiCl_4$,2NOCl	W., R.W.	15·2	65·64	—	14·93	66·33	—
			Sn.			Sn.		
Sn	$SnCl_4$,2NOCl	S.	29·71	53·49	—	30·37	54·35	7·16
$SnCl_2$	$SnCl_4$,2NOCl	—	29·82	53·91	6·51	—	—	—
$SnCl_4$	$SnCl_4$,2NOCl	W., R.W., A.	29·92	53·85	7·08	—	—	—
			Mn.			Mn.		
$MnCl_2$	$MnCl_2$,NOCl	G.M., A.	28·71	54·95	7·51	28·73	55·62	7·31
			Fe.			Fe.		
Fe	$FeCl_3$,NOCl	S.	24·18	62·50	—	24·53	62·30	6·15
$FeCl_3$	$FeCl_3$,NOCl	W., G.M.	24·29	62·60	6·3	—	—	—
$FeCl_2$	$FeCl_3$,NOCl	G.M.	24·7	62·07	6·4	—	—	—

The Reaction with Aluminium.—Nitrosyl chloride was condensed on very fine aluminium powder; at −40° there was no reaction but at −20° reaction occurred with incandescence. 0·5 G. of very fine aluminium wire was cooled to −60° and excess of nitrosyl chloride added; a very vigorous reaction took place on warming to about −20°, nitric oxide being evolved. Vigorous reaction occurred with strips of aluminium foil at −40° but could be controlled by further cooling. After standing in contact with nitrosyl chloride for 14 hours a red syrupy liquid was obtained; when warmed to 30° to remove excess of nitrosyl chloride, this gave a yellow solid which evolved nitric oxide with water and appeared to be identical with that obtained from aluminium chloride. The aluminium was precipitated as hydroxide and ignited to oxide (Found: Al, 14·21, 14·34; Cl, 71·01; N, 6·7. Calc. for $AlCl_3$,NOCl: Al, 13·62; Cl, 71·30; N, 7·04%).

The Reaction with Aluminium Chloride.—Nitrosyl chloride was condensed at −20° on 1·0 g. of iron-free, resublimed aluminium chloride and allowed to stand at this temperature for six hours; excess was removed from the viscous red syrup as above (Found: Al, 13·92; Cl, 71·83; N, 7·05%). The lemon-yellow compound evolved nitrosyl chloride on standing for 3—4 minutes in air, leaving a white residue of aluminium chloride. With a small amount of water, nitric oxide was evolved, and the aluminium chloride formed rapidly dissolved when a further drop of water was added. A small quantity of $AlCl_3$,NOCl was sublimed at atmospheric pressure in a current of dry nitrogen. In a sealed tube it melted with decomposition at 109—112°.

Action of Nitrosyl Chloride on Gallium.—Nitrosyl chloride was condensed on 0·4 g. of gallium at −50°; no reaction occurred but at −30° nitric oxide was evolved and the metal dissolved to a black solution. The reaction continued for some time even when the tube was placed in solid carbon dioxide. At room temperature considerable heat was evolved. On heating on a water-bath the liquid separated into two layers, the lower plum-coloured, the upper black (gallium chloride melts at 77°). On shaking, the two layers mixed and did not separate on cooling or on standing for several weeks. At room temperature a viscous red liquid was obtained which tenaciously retained nitrosyl chloride. The tube was warmed at 60°, whereupon excess of nitrosyl chloride was readily evolved, giving a yellow crystalline *solid* which was immediately sealed for analysis. It was extremely deliquescent, forming a colourless liquid in a matter of seconds. The gallium was estimated by sulphite hydrolysis (Dennis and Bridgman, *J. Amer. Chem. Soc.*, 1918, **40**, 1531), the gallium hydroxide being obtained in a granular, easily filtrable form (Found: Ga, 29·77, 29·63; Cl, 58·2. $GaCl_3$,NOCl requires Ga, 28·84; Cl, 58·75%).

Reaction with Gallium Trichloride.—Gallium trichloride was prepared by passing dry, air-free hydrogen chloride over the metal (1 g.) in the boat (Fig. 2), and the temperature was slowly raised to 200°. The exit end of the tube was protected with phosphoric oxide. After 3 hours (40 bubbles/min.) all the gallium had reacted. The apparatus was swept out with nitrogen, and the gallium trichloride melted and run into the side-arm *A*, which was cooled in solid carbon dioxide, and nitrosyl chloride passed in. The tube was then sealed off along *ab*. The trichloride was very soluble in nitrosyl chloride, forming a red solution (Found: Ga, 29·0, 30·28; Cl, 58·1. $GaCl_3$,NOCl requires Ga, 28·84; Cl, 58·75%).

Action of Nitrosyl Chloride on Indium.—At room temperature in a sealed tube there was a slight reaction between 1·2 g. of fine indium shavings and nitrosyl chloride. A yellow outside layer formed which prevented further action. The tube was heated at 100° for 5 days, a further portion then being attacked, but a large amount of indium was unchanged. The solution in water gave characteristic In^{3+} reactions.

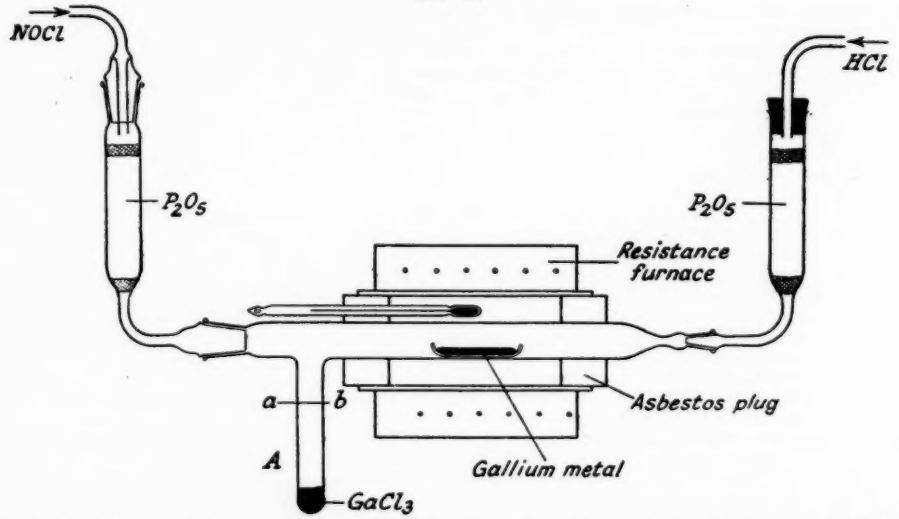
Indium dichloride was prepared by passing dry, air-free hydrogen chloride over molten indium; the metal changed to a reddish-brown colour, then clear yellow, and volatilised completely, a white powder being deposited on the cold parts of the tube. At room temperature vigorous reaction occurred between indium dichloride and nitrosyl chloride, the solid turning yellow, then orange. After 4 days' standing, a yellow deliquescent solid was obtained which dissolved readily in a small amount of water, evolving nitric oxide. It was stable in dry air with no tendency to evolve nitrosyl chloride; when gently heated, it evolved nitrosyl chloride and the white residue dissolved completely in water, no grey indium being deposited. On stronger heating the residue sublimed forming white plates in the upper part of the tube (Found: In, 51·45. Calc. for $InCl_3$: In, 51·87%). The sublimate was sealed with nitrosyl chloride

and on heating dissolved completely to a red solution; on cooling, yellow flakes separated, giving the same yellow solid as previously. Indium was determined by a modification of the method of Moser and Siegmann (*Monatsh.*, 1930, **55**, 14).

A weighed amount of the *compound* (*ca.* 0·2 g.) was decomposed with 150 ml. of water, 3 drops of methyl-orange added, dilute ammonia (1 : 10) run in dropwise from a burette until the indicator turned yellow, and the solution heated to boiling; then 1 ml. excess of ammonia was added, the liquid being stirred all the time. The flocculent precipitate of indium hydroxide, on being gently warmed and stirred, became granular and compact. It was filtered off, and washed with a small quantity of hot water until free from chloride (the sesquioxide is volatile in the presence of chlorides), and the filter-paper and residue carefully dried and ignited below 700°. After acidification with nitric acid, chlorine was determined in the filtrate in the usual way [Found: (*a*) In, 39·31; Cl, 49·06; Cl/In = 4·03. (*b*) In, 39·62; Cl, 49·04; Cl/In = 4·0. (*c*) Cl, 48·28. (*d*) N, 4·0. $InCl_3$,NOCl requires In, 40·02; Cl, 49·51; N, 4·8%].

Indium monochloride. A weighed quantity of the dichloride (1·0 g.) was introduced into a thick "Pyrex" tube, a slight excess (10%) of indium shavings added, and the tube sealed, shaken, and warmed with a small burner. The contents rapidly formed a dark red, almost black, liquid which was kept in the molten state for several minutes. On cooling, it solidified to a light red solid. The mixture was gently heated in a porcelain boat in a stream of dry nitrogen; orange-red monochloride sublimed, leaving a grey bead of excess indium. Indium monochloride reacted with nitrosyl chloride in a sealed tube at room temperature, turning yellow, and the supernatant liquid became black immediately. When the compound was heated in a water-bath, the nitrosyl chloride became cherry-red but became black again on cooling and shaking: $InCl + 3NOCl = InCl_3,NOCl + 2NO$ (Found: Cl, 48·97%).

FIG. 2.



Indium trichloride was prepared by passing a current of dry, air-free chlorine over the heated dichloride at 370°. The trichloride sublimed as pearly white plates in the colder parts of the tube. It dissolved completely in water, with no trace of indium due to hydrolysis of unchanged indium dichloride. 1·5 G. of indium trichloride rapidly absorbed nitrosyl chloride, turning yellow immediately. The addition compound was fairly soluble in liquid nitrosyl chloride but not to the same extent as the aluminium, gallium, or thallium compound. On gentle heating, nitrosyl chloride was evolved and indium trichloride could be obtained as previously (Found: In, 39·26, 39·29; Cl, 49·25%; Cl/In = 4·05).

Indium tribromide. Indium tribromide was prepared by heating indium in a current of bromine and nitrogen. Bromination took place through the monobromide (dark red) and dibromide (colourless). The product depended to some extent on the temperature; at 200° the dibromide was obtained after 4½ hours' passage of bromine. At 370° indium tribromide sublimed as pearly white hexagonal plates (the largest 0·7 cm.) which were sublimed twice in dry nitrogen; yield 90—95% (Found: In, 32·21; Br, 67·81. Calc. for $InBr_3$: In, 32·35; Br, 67·65%). Reaction occurred between indium tribromide and nitrosyl chloride at room temperature, the solid turned yellow, the supernatant liquid black. On being heated in a water-bath it partly dissolved, crystallising on cooling. After removal of excess of nitrosyl chloride a reddish-brown solid remained which, when gently warmed by the hand, evolved bromine. The yellow solid remaining contained no bromine (Found: Cl/In = 4·07).

Indium monobromide, prepared by warming the tribromide with indium shavings, was sublimed in nitrogen as for the monochloride. The carmine indium monobromide was not deliquescent; on addition of water there was no immediate reaction, but it turned grey, due to the separation of indium, after 15 minutes, forming a solution of the tribromide. With nitrosyl chloride the solid turned yellow, and after 2 days' heating on a water-bath the yellow $InCl_3$,NOCl was obtained. There was no trace of bromide in the residue.

Preparation of Thallium Compounds.—The thallium compounds used were prepared from thallous sulphate; all precautions were taken to ensure pure products.

The Action of Nitrosyl Chloride on Thallous Chloride.—Excess of nitrosyl chloride was condensed on to 1 g. of thallous chloride at −30°. No reaction occurred after one hour, but at −20°, reaction took place, nitric oxide was evolved, and the substance turned yellow. It was left for 14 hours at −20°. The yellow solid appeared to be homogeneous under a microscope. It was not deliquescent and was insoluble in cold water. It dissolved in hot water to form a colourless solution which on cooling deposited glittering hexagonal plates, which could be recrystallised from water with three drops of concentrated nitric acid without hydrolysis. Since Tl^{3+} interferes with chlorine estimation as silver chloride, it was removed before the addition of silver nitrate.

A weighed amount of the compound (*ca.* 0·2 g.) was washed into 300 ml. of water and a few drops of dilute nitric acid and heated to boiling. The solution was cooled to room temperature, and the Tl^{3+} removed by precipitation with potassium hydroxide solution. The residue was washed with hot water, and the filtrate acidified with dilute nitric acid and precipitated with silver nitrate.

Determination of thallium. Precipitation as thallous chromate was used. About 0·2 g. of the substance was dissolved in 100 ml. of water, 10 ml. of sulphurous acid added, and the whole stirred and allowed to stand for a day to reduce Tl^{3+} to Tl^{+}. Excess of sulphur dioxide was boiled off, the solution cooled, neutralised with ammonia, heated to 80°, and 2 g. of potassium chromate added (10% soln.) with constant stirring. After standing at room temperature for 2 days, the precipitate was collected in a Gooch crucible, washed with 1% potassium chromate solution, then with 50% alcohol, and dried at 120° to constant weight [Found (in product straight from reaction): Cl, 19·2, 20·98; (in recrystallised product): Cl, 21·73, 21·99; Tl, 78·71, 79·07; Cl/Tl = 1·49. Calc. for $3TlCl,TlCl_3$, *i.e.*, Tl_2Cl_3: Cl, 20·67; Tl, 79·33; Cl/Tl = 1·5]. Thus the product before and after recrystallisation was Tl_2Cl_3.

Action of Nitrosyl Chloride on Thallium.—Metallic thallium was unattacked by nitrosyl chloride at room temperature, but when heated to 100° for 5 days it formed a yellow solid. The nitrosyl chloride became black when viewed through 0·75 cm. On cooling in solid carbon dioxide, yellow crystals separated from the solution. The solid was very deliquescent but did not evolve nitrosyl chloride at room temperature; it dissolved completely even in a small amount of water, evolving nitric oxide. Thallium was determined after reduction, and chloride after removal of Tl^{3+} (Found: Tl, 53·89, 53·8; Cl, 37·24, 37·04; Cl/Tl = 3·9; N, 3·36. $TlCl_3,NOCl$ requires Tl, 54·29; Cl, 37·73; N, 3·72%). The yellow *solid* was qualitatively examined for Tl^{+}. The solution was made alkaline with 3% potassium hydroxide solution, and the bulky brown precipitate of hydrated Tl_2O_3 filtered off and washed with hot water. Potassium chromate did not give a precipitate in the filtrate (*i.e.*, no Tl^{+} present). In a similar reaction with Tl_2Cl_3 the presence of Tl^{+} as well as Tl^{3+} could readily be detected.

The Incomplete Reaction of Thallium with Nitrosyl Chloride.—The two reagents were heated together at 100° for 1 day. The top part of the solid consisted of the yellow addition compound; at the bottom of the tube a yellow solid remained (with unchanged thallium) which was insoluble in cold water, but soluble in hot water, forming yellow hexagonal plates on cooling (Found: Tl, 79·69. Calc. for Tl_2Cl_3: Tl, 79·33%).

Reaction between Tl_2Cl_3 *and Nitrosyl Chloride.*—On heating Tl_2Cl_3 with nitrosyl chloride for 6 hours it dissolved completely, forming a red solution. On removal from the tube and shaking, the liquid turned black: $Tl_2Cl_3 + 5NOCl = 2(TlCl_3,NOCl) + 3NO$. After removal of the excess of nitrosyl chloride the addition compound was obtained which gave no Tl^{+} reaction.

Reaction between Nitrosyl Chloride and Thallous Chloride at 100°.—1·2 G. of thallous chloride and 5 ml. of nitrosyl chloride, heated for 3 days at 100°, formed a black solution. On cooling, the solid separated slowly and there was some tendency to supersaturation. The yellow *compound* contained no Tl^{+} (Found: Tl, 54·71; Cl, 37·83%; Cl/Tl = 3·98).

Reaction between Nitrosyl Chloride and Thallous Oxide.—Thallous hydroxide was prepared by double decomposition of thallous sulphate and carbonate-free barium hydroxide. The crystals were partly dehydrated in a desiccator over phosphoric oxide, then heated to 120° in a steady current of dry nitrogen.

At −20° nitrosyl chloride reacted very slowly with thallous oxide, but at −10° nitric oxide was evolved and the solid turned yellow. The temperature was kept at −10° to −20° for 48 hours, and excess of nitrosyl chloride distilled off, leaving a yellow solid which could be recrystallised from dilute nitric acid in characteristic crystals of Tl_2Cl_3.

Nitrosyl chloride was heated with 1 g. of thallous oxide at 100° for 10 hours. The solid product reacted with water, evolving nitric oxide and precipitating Tl_2Cl_3. It was quickly broken up, more nitrosyl chloride added, and the tube resealed and heated for 3 days. The yellow solid then obtained dissolved completely even in a small amount of water (Found: Tl, 54·99%).

Action of Nitrosyl Chloride on Thallous Nitrate.—Nitrosyl chloride was condensed on to 1 g. of the nitrate at −20°, and after 20 hours excess of nitrosyl chloride was evaporated off at about 5°. The solid obtained was orange; about 0·5 ml. of brown-red liquid remained, which smelt of nitrogen dioxide; this was boiled off into sodium hydroxide solution which gave good nitrite and nitrate reactions. After 5 hours in an evacuated desiccator over phosphoric oxide the orange solid turned yellow and could be recrystallised as Tl_2Cl_3: $TlNO_3 + NOCl = TlCl + N_2O_4$.

Action of Nitrosyl Chloride on Thallous Nitrate.—When these reagents were heated to 100° the liquid turned black, and the solid dissolved completely, separating out as very small hexagonal crystals on cooling (Found: Tl, 53·84%). From the black excess of nitrosyl chloride green "dinitrogen trioxide" could be distilled.

Action of Nitrosyl Chloride on Thallous Nitrite.—The nitrite was prepared by double decomposition of the sulphate with barium nitrite. Evaporation of the solution at 80° gave a light orange solid. The concentrated solution was pale yellow, the dilute colourless.

At −20° thallous nitrite rapidly absorbed nitrosyl chloride; the orange solid turned yellow, and recrystallisation gave Tl_2Cl_3.

1 G. of thallous nitrite was heated with nitrosyl chloride on a water-bath for 3 days. After excess of the latter had been boiled off, about ½ ml. of dinitrogen tetroxide remained. The yellow addition *compound* dissolved completely in water (Found: Tl, 53·89%).

Reaction between Nitrosyl Chloride and Thallous Bromide.—The bromide was sealed with the chloride

and heated on a water-bath for 4 days. It dissolved completely and hexagonal crystals separated on cooling (Found: Tl, 54·49; Cl, 36·7%; Cl/Tl = 3·88).

Reaction between Nitrosyl Chloride and Thallous Iodide.—When 1 g. of the iodide was heated with nitrosyl chloride, it remained yellow and the liquid became black; on further heating, a black solution was formed, from which small hexagonal crystals separated after cooling. A black solid remained which reacted with water liberating iodine; this was extracted three times with carbon tetrachloride The aqueous solution was made alkaline with sodium hydroxide, warmed, and filtered, and the filtrate gave no reaction for Tl^+.

Action of Nitrosyl Chloride on Thallic Chloride.—Crystalline hydrated thallic chloride placed over phosphoric oxide at 20 mm. pressure for 1 week dissolved in the water of crystallisation, and then solidified to a white powder. Chloride was estimated after removal of Tl^{3+} by sodium hydroxide (Found: Cl, 33·95. Calc. for $TlCl_3$: Cl, 34·26%). Nitrosyl chloride was condensed on anhydrous thallic chloride at −20°. The solid rapidly absorbed the first few drops and became yellow, but it dissolved on shaking with more liquid, forming a red solution, which deposited small hexagonal crystals on cooling. The solid appeared to be identical with that obtained from thallium metal (Found: Cl, 37·55%).

Conclusions.—(1) The following compounds have been confirmed: CuCl,NOCl, $ZnCl_2$,NOCl, $HgCl_2$,NOCl, $TiCl_4$,2NOCl, $SnCl_4$,2NOCl, $MnCl_2$,NOCl, $FeCl_3$,NOCl.

(2) The action of nitrosyl chloride on Ga and $GaCl_3$ gave the new compound $GaCl_3$,NOCl.

(3) Indium or its chlorides or bromides gave a new compound, $InCl_2$,NOCl.

(4) Compounds described by Sudborough (TlCl,$TlCl_3$,2NOCl) and Cuttica *et al.* ($TlCl_2$,3NOCl) are really $TlCl_3$,NOCl.

(5) Contrary to Sudborough's results, it was found that aluminium and aluminium chloride both form $AlCl_3$,NOCl with nitrosyl chloride.

The authors thank Professor R. P. Linstead, C.B.E., F.R.S., of the Chemical Research Laboratory, Teddington, for the loan of gallium metal, and Imperial Chemical Industries Ltd. for a gift of nitrosyl chloride. One of them (A. L. W.) is indebted to East Suffolk Education Committee for a maintenance grant.

QUEEN MARY COLLEGE (UNIVERSITY OF LONDON). [*Received, December 22nd,* 1947.]

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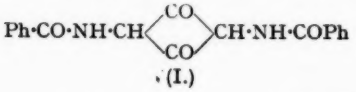
397. "*Dibenzamidodioxytetrol.*"

By J. W. CORNFORTH and H. T. HUANG.

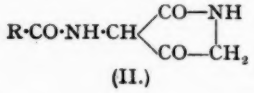
The structure (III; R = Ph) for a product obtainable from various hippuric acid derivatives is confirmed.

AN acidic substance $C_{18}H_{14}O_4N_2$, first obtained (Rügheimer, *Ber.*, 1888, **21**, 3325; 1889, **22**, 1954) from ethyl hippurate with sodium or sodium ethoxide, has since been obtained in many other ways, though not always recognised by the workers concerned. Rügheimer named it "dibenzamidodioxytetrol", for its reactions led him to conclude that it was an enolised form of 2 : 4-diketo-1 : 3-dibenzamido*cyclo*butane (I). Hydrolysis or alcoholysis leads to the loss on one benzoyl group and the product, $C_{11}H_{10}O_3N_2$, was formulated by Rügheimer as 3-benzamido-2 : 4-diketopyrrolidine (II; R = Ph) as the alternative amino*cyclo*butanedione structure was not in accord with the properties; the formation of (II; R = Ph) from (I) was held to be a hydrolytic ring-fission followed by lactam formation.

The evidence relating to these two substances has been discussed by one of us ("The Chemistry of Penicillin," Chap. XXI) and it was concluded that the substance $C_{18}H_{14}O_4N_2$ was probably 3-benzamido-2 : 4-diketo-1-benzoylpyrrolidine (III; R = Ph).



(I.)



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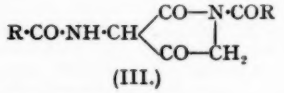
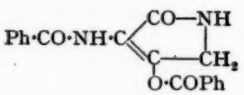
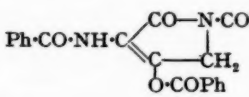


(III.)

(IV.)





(V.)

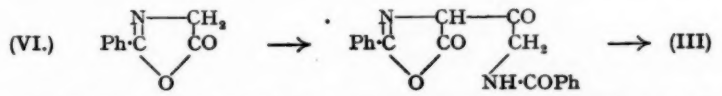
Benzoylation of (II; R = Ph) with benzoyl chloride and pyridine has now been found to give a new substance which, from the absence of acidity and negative ferric chloride test, was 3-*benzamido*-2-*keto*-4-*benzoyloxy*-Δ^3-*pyrroline* * (IV). With benzoic anhydride, however, two benzoyl groups were introduced and the *product*, evidently (V), was identical with a substance obtained from Rügheimer's $C_{18}H_{14}O_4N_2$ compound with benzoyl chloride and pyridine. It is

* This substance was prepared independently by Dr. A. H. Cook (personal communication).

thereby confirmed that the substances $C_{18}H_{14}O_4N_2$ and $C_{11}H_{10}O_3N_2$ have the same nucleus, and the structure (III; R = Ph) for the former is no longer in doubt.

Catalytic hydrogenation of (II; R = Ph) led to 3-*hexahydrobenzamido*-2 : 4-*diketopyrrolidine* (II; R = C_6H_{11}); the resistance of the pyrrolidione ring to reduction is noteworthy. Boiling acetic anhydride displaced a benzoyl group from (II; R = Ph) and the product was apparently identical with the 3-acetamido-2 : 4-diketo-1-acetylpyrrolidine (III; R = Me) obtained by Brodrick and Peak ("The Chemistry of Penicillin," Chap. XXI) from 3-hexamido-2 : 4-diketopyrrolidine (II; R = C_5H_{11}) and acetic anhydride.

The formation of (III; R = Ph) from ethyl hippurate and sodium ethoxide doubtless proceeds by lactam formation from the intermediate ethyl α-hippurylhippurate. The formation from 2-phenyloxazolone (VI), induced by various reagents (Cook, Elvidge, Heilbron, and Levy, "The Chemistry of Penicillin," Chap. XXI; Bailey, Baker, and Bradley, *ibid.*), may proceed as follows:



The formation of (III; R = Ph) from hippurazide and alkali (Curtius and Lenhard, *J. pr. Chem.*, 1904, **70**, 240) and from hippuryl chloride in various ways (Scheiber and Reckleben, *Ber.*, 1913, **46**, 2413; Karrer and Itschner, *Helv. Chim. Acta*, 1932, **15**, 420) may well involve the oxazolone (VI) as intermediate.

Experimental.

Preparation of Materials.—The compound $C_{18}H_{14}O_4N_2$ was prepared by the methods of Rügheimer and of Karrer and Itschner (*locc. cit.*). The hemihydrate separated from ethanol in slender needles, m. p. 116° (Found: C, 65·4; H, 4·6. Calc. for $C_{18}H_{14}O_4N_2,0{\cdot}5H_2O$: C, 65·3; H, 4·5%). The hydrolysis product $C_{11}H_{10}O_3N_2$ was recrystallised from ethanol; white plates, m. p. 205° (Found: C, 60·2; H, 4·6. Calc. for $C_{11}H_{10}O_3N_2$: C, 60·6; H, 4·6%). On shaking the latter product with 2 : 4-dinitrophenylhydrazine in 5N-hydrochloric acid for 2 days, a 2 : 4-*dinitrophenylhydrazone* was obtained; dull red prisms from pyridine, m. p. above 310° (Found: N, 21·3. $C_{17}H_{14}O_6N_6$ requires N, 21·1%).

Benzoylation of (II) *and* (III; R = Ph).—(*a*) Benzoyl chloride (0·2 c.c.) was added dropwise to a cooled solution of 3-benzamido-2 : 4-diketopyrrolidine (0·3 g.) in pyridine (3 c.c.). After ½ hour ether (10 c.c.) was added, and the product collected, dried (0·3 g.), and recrystallised twice from ethanol–acetic acid, giving 3-*benzamido*-2-*keto*-4-*benzoyloxy*-Δ^3-*pyrroline*: slender silky needles, m. p. 230°, insoluble in aqueous sodium carbonate and giving no colour with ferric chloride in alcohol (Found: C, 66·7; H, 4·4; N, 8·6. $C_{18}H_{14}O_4N_2$ requires C, 67·1; H, 4·4; N, 8·7%). The substance (50 mg.) was warmed with sodium hydroxide (1 c.c. of N) until solution was complete; acidification then gave 3-benzamido-2 : 4-diketopyrrolidine (II; R = Ph), m. p. and mixed m. p. 205° after recrystallisation.

(*b*) 3-Benzamido-2 : 4-diketopyrrolidine (0·2 g.) was refluxed gently with benzoic anhydride (1 g.) for 5 hours. After being cooled and washed with ether, the insoluble residue (200 mg.) was collected and recrystallised from ethanol–acetic acid, giving 3-*benzamido*-2-*keto*-4-*benzoyloxy*-1-*benzoyl*-Δ^3-*pyrroline* (V), fine needles m. p. 185—186° (Found: C, 70·7; H, 4·3. $C_{25}H_{18}O_5N_2$ requires C, 70·4; H, 4·3%). The substance was neutral and gave no colour with alcoholic ferric chloride.

(*c*) 3-Benzamido-2 : 4-diketo-1-benzoylpyrrolidine (III; R = Ph; 170 mg.) in pyridine (1·5 c.c.) was chilled and treated with benzoyl chloride (0·1 c.c.). After one hour ether (10 c.c.) was added, and the crystalline product (150 mg.) collected. Recrystallisation from ethanol–acetic acid gave the benzoyl derivative (V); m. p. and mixed m. p. 185—186°.

3-*Acetamido*-2 : 4-*diketo*-1-*acetylpyrrolidine* (III; R = Me).—The diketopyrrolidine (II; R = Ph; 200 mg.) was refluxed with acetic anhydride (3 c.c.) for 4 hours. Water (10 c.c.) was then added, and the mixture when homogeneous was evaporated at low pressure. Five recrystallisations of the residue from ethanol gave the diketopyrrolidine (III; R = Me); platelets (100 mg.), m. p. 218° (Brodrick and Peak, *loc. cit.*, gave m. p. 218°), soluble in aqueous sodium hydrogen carbonate and giving a violet colour with ethanolic ferric chloride (Found: C, 48·5; H, 5·1; N, 14·4. Calc. for $C_8H_{10}O_4N_2$: C, 48·5; H, 5·1; N, 14·1%).

Hydrogenation of (II; R = Ph).—The diketopyrrolidine (697 mg.) and platinum oxide (100 mg.) suspended in methanol (15 c.c.) were hydrogenated at 15°/1 atm.; reduction was still proceeding slowly after 18 hours, when the hydrogen consumed was equivalent to 4 atoms per molecule of (II; R = Ph). The mixture was warmed, and the catalyst and solvent removed. The solid residue dissolved completely in N-sodium hydroxide. Saturation of this solution with carbon dioxide precipitated (incompletely) 3-*hexahydrobenzamido*-2 : 4-*diketopyrrolidine* (II; R = C_6H_{11}); most of the product remained in solution along with unreduced material. The hydrogenation product crystallised from methanol in needles, m. p. 203—204° depressed by (II; R = Ph) to 180—190° (Found: C, 59·2; H, 7·1; N, 11·9. $C_{11}H_{16}O_3N_2$ requires C, 58·9; H, 7·2; N, 12·5%). With alcoholic ferric chloride it gave a deep blue colour.

We thank the British Council for enabling H. T. H. to participate in this work.

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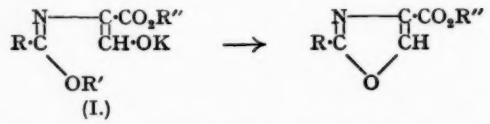
398. *Further Studies of Oxazoles and Glyoxalines.*

By J. W. Cornforth and H. T. Huang.

The condensation of imido-ethers with α-amino-ketone hydrochlorides is shown to produce both oxazoles and glyoxalines. Some observations are recorded on the synthesis of glyoxalines from oxazole-4-carboxylic acids.

In a recent memoir (Cornforth and Cornforth, *J.*, 1947, 96) a synthesis of oxazoles was described, in which the determining stage was the cyclisation by acid of a potassium enolate of type (I).

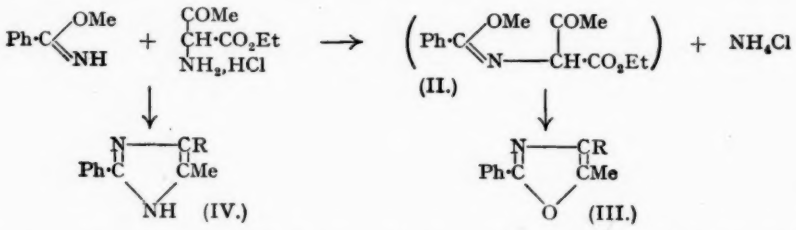


(I.)

It was suggested on the basis of these experiments that oxazoles might well result from the reaction of imido-ethers with α-amino-carbonyl compounds. This possibility has now been investigated.

Benzimidomethyl ether and ethyl α-aminoacetoacetate hydrochloride were chosen as reactants for the first trial. The imido-ether was added to a solution of the hydrochloride in acetic acid at 100°. Condensation took place readily, and the product was separated into a neutral and a basic fraction. The neutral part consisted mainly of benzamide and ethyl 2-phenyl-5-methyloxazole-4-carboxylate, which was characterised by hydrolysis to 2-phenyl-5-methyloxazole-4-carboxylic acid (III; R = CO_2H) and decarboxylation of the latter to 2-phenyl-5-methyloxazole (III; R = H).

The basic product from its composition and properties was evidently *ethyl 2-phenyl-5-methylglyoxaline-4-carboxylate* (IV; R = CO_2Et). Apparently reaction between the imido-ether and the amino-ketone hydrochloride can take place in two ways:



(II.) (IV.) (III.)

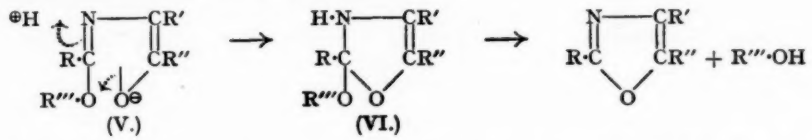
It is also possible, though less likely, that the glyoxaline (IV; R = CO_2Et) is derived from ammonium chloride and the intermediate (II). Hydrolysis of (IV; R = CO_2Et) gave the expected *2-phenyl-5-methylglyoxaline-4-carboxylic acid* (IV; R = CO_2H), which lost carbon dioxide on heating and furnished 2-phenyl-4-methylglyoxaline (IV; R = H).

The nature of the various substances which have been described in the literature as 2-phenyl-4-methylglyoxaline (VII) was discussed in an earlier paper (Cornforth and Huang, this vol., p. 731). The identity of the present specimen was checked by a synthesis from benzamidine and chloroacetone (method of Kunckell, *Ber.*, 1901, **34**, 631), which gave a product identical with our glyoxaline. The properties agreed well with those of the compound obtained by John (*Ber.*, 1935, **68**, 2290) as a by-product in the preparation of 2-styryl-4-methylglyoxaline from cinnamaldehyde and methylglyoxal; and John's formulation of this compound as (IV; R = H) is thereby confirmed. It may be mentioned that an attempt to prepare (IV; R = H) from methylglyoxal and benzaldehyde led to an intractable mixture.

Condensation of heximidomethyl ether with ethyl α-aminoacetoacetate hydrochloride proceeded smoothly; from the neutral product *5-methyl-2-amyloxazole-4-carboxylic acid* was obtained after hydrolysis, and the basic product consisted essentially of *ethyl 5-methyl-2-amylglyoxaline-4-carboxylate*. A further extension of the synthesis was found in the reaction of benzimidomethyl ether and aminoacetone hydrochloride; the process went as smoothly as before and 2-phenyl-5-methyloxazole (III; R = H) was isolated, along with 2-phenyl-4-methylglyoxaline. However, when an attempt was made to condense benzimidomethyl ether with aminoacetaldehyde hydrochloride, a tarry product resulted from which only 2 : 4 : 6-triphenyltriazine could be extricated. This last result was evidently due to the instability of

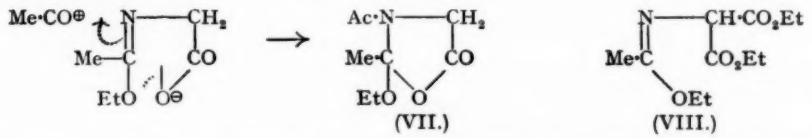
aminoacetaldehyde. No search has so far been made for conditions which would favour the production in this synthesis of oxazoles alone, or of glyoxalines alone.

Sufficient data are now available to discuss the mode of formation of the oxazole ring in this type of synthesis. Cyclisation appears only to take place under acid conditions: salts of the general formula (I) have shown no tendency to spontaneous cyclisation. The process may therefore be initiated by the acceptance of a proton (or other cation) by the nitrogen atom of the enolate ion (V), followed by a rearrangement of electrons to give the intermediate (VI), which passes to the oxazole by loss of alcohol.



(V.) (VI.)

An intermediate analogous to (VI), *viz.*, 5-keto-2-ethoxy-3-acetyl-2-methyltetrahydrooxazole (VII), appears to have been produced in this manner from potassium 1-ethoxyethylideneaminoacetate and acetyl chloride (Cornforth and Cornforth, *loc. cit.*).



(VII.) (VIII.)

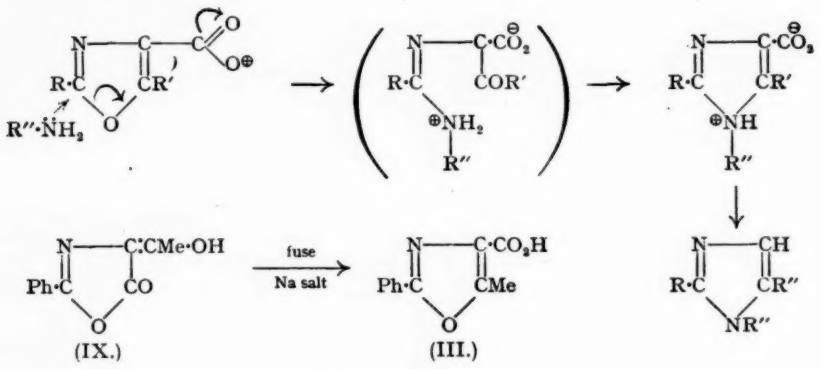
In the same paper, the preparation of ethyl 1-ethoxyethylideneaminomalonate (VIII) was described; this could be distilled unchanged and it has since been found that treatment with boiling acetic acid or anhydride had no effect on (VIII). Treatment of (VIII) with potassium ethoxide in ether and addition of the resulting potassium compound to boiling acetic acid gave ethyl acetamidomalonate as the only identifiable product. Vigorous treatment of (VIII) with sulphuric acid gave ethyl aceturate and a small quantity of an unidentified base (isolated as the *picrate*). Degeneracy of the anion of (VIII) may be the cause of this failure to cyclise: it is possible that a sufficiently high negative charge cannot be transferred to one of the carbonyl oxygen atoms to allow formation of the intermediate (VI). Alternatively, it may be that the " aromatic " stabilisation of 5-alkoxyoxazoles is not so great as that of simple oxazoles, so that loss of alcohol from the intermediate (VI) does not take place so readily.

The condensation of benzimidomethyl ether with chloroacetone was tried, in order to find out whether the resulting oxazole, if one were formed, would be 2-phenyl-4- or -5-methyloxazole. The former was the product actually obtained; a considerable amount of benzamide was also formed and it is possible that the oxazole was produced by condensation of chloroacetone with some of the benzamide. It is noteworthy that a mixture of the picrates of 2-phenyl-4- and -5-methyloxazole showed little depression in melting point. Since the individual picrates have almost the same melting point, this is a potential source of confusion.

A synthesis of glyoxalines from oxazole-4-carboxylic acids and ammonia (or aniline) has been reported (Cornforth and Cornforth, *loc. cit.*). It was of interest to determine whether the oxazoles resulting from decarboxylation of such acids would form glyoxalines with equal facility. Accordingly, 2-amyloxazole and 2-amyloxazole-4-carboxylic acid were heated with aqueous ammonia under identical conditions. At a temperature not exceeding 150° the acid was completely destroyed with formation of 2-amylglyoxaline, whereas the oxazole was recovered entirely unchanged. It is therefore certain (i) that this glyoxaline synthesis does not proceed by way of an initial decarboxylation, and (ii) that the carboxyl group facilitates the amination, presumably as on p. 1962.

A synthesis of 2-phenyl-4-methylglyoxaline in three stages from hippuric acid has been worked out, and found to be much the most satisfactory way of preparing (IV; R = H) especially in quantity. The preparation of 2-phenyl-4-(1-hydroxyethylidene)-4 : 5-dihydrooxazol-5-one (IX) from sodium hippurate and acetic anhydride has been described by Attenburrow, Elliott, and Penny (this vol., p. 310). The sodium salt of this oxazolone rearranged smoothly on melting (cf. Cornforth and Cornforth, " The Chemistry of Penicillin," Chap. XXI) to give the sodium salt of 2-phenyl-5-methyloxazole-4-carboxylic acid (III; R = CO_2H), which gave (IV; R = H) when heated with aqueous ammonia under pressure. The yields were good, and it seems that this iminazole synthesis is particularly well suited to the preparation of

2-arylglyoxalines; in this respect it is complementary to the old glyoxaline synthesis. If an iminazole unsubstituted in the 4(5)-position is required, the appropriate aroylglycine is condensed with ethyl orthoformate–acetic anhydride to give a 4-hydroxymethyleneoxazolone (cf. "The Chemistry of Penicillin"); rearrangement and amination then follow as before. This process has already been used to prepare 2-phenylglyoxaline; details will be published elsewhere.



(IX.) (III.)

Experimental.

Condensation of Benzimidomethyl Ether with Ethyl α-Aminoacetoacetate Hydrochloride.—The imido-ether (1·5 c.c.) was added during one minute to a stirred solution of the hydrochloride (2 g.) in glacial acetic acid (4 c.c.) at 100°. A strong smell of ethyl benzoate was observed, and a yellow precipitate appeared almost at once. After being kept at room temperature for 20 minutes, the mixture was cooled in ice, diluted with water, and extracted repeatedly with ether (total 30 c.c.). The ethereal extract was washed with hydrochloric acid (15 c.c. of N). The acid solution on neutralisation with sodium carbonate gave a precipitate (0·25 g.); a further quantity (50 mg.) was obtained by neutralising the aqueous acetic acid solution. The dried precipitate was recrystallised from benzene, giving *ethyl 2-phenyl-5-methylglyoxaline-4-carboxylate* (IV; R = CO_2Et) in long thin needles, m. p. 199—199·5° unchanged by further crystallisation (Found: C, 67·8; H, 6·1; N, 12·2. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·1; N, 12·0%). The compound was soluble in most organic solvents.

After the acid washing, the ethereal solution was washed with dilute sodium hydroxide solution, dried ($MgSO_4$), and evaporated. On distillation a low-boiling fraction (0·5 g.) was collected at 70—80°/15 mm.; the higher fraction distilled at 95°/0·05 mm. and partly solidified. The oil (0·3 g.) was separated by filtration from the embedded solid (identified as benzamide, m. p. 126°) (Found: C, 69·5, H, 5·8. Calc. for C_7H_7ON: C, 69·4; H, 6·1%) and redistilled thrice; it then consisted essentially of ethyl 2-phenyl-5-methyloxazole-4-carboxylate (Found: C, 67·2; H, 5·9. Calc. for $C_{13}H_{13}O_3N$: C, 67·5; H, 5·7%).

This ester (0·8 g.) was heated with potassium hydroxide (2·8 g.) in water (30 c.c.) on the steam-bath. A clear solution was obtained in 15—20 minutes; after cooling the liquor was washed with ether, warmed to expel dissolved ether, cooled in ice, and acidified to Congo-red with hydrochloric acid. The crystalline precipitate (0·69 g., m. p. 180°) had m. p. 181° after recrystallisation from benzene (Found: C, 64·7; H, 4·3; N, 6·9. Calc. for $C_{11}H_9O_3N$: C, 65·0; H, 4·4; N, 6·8%). Elliott ("The Chemistry of Penicillin," Chap. XXI), records m. p. 181° for 2-phenyl-5-methyloxazole-4-carboxylic acid (III; R = CO_2H) prepared by cyclodehydration of ethyl α-benzamidoacetoacetate followed by hydrolysis of the ester.

2-Phenyl-5-methyloxazole.—2-Phenyl-5-methyloxazole-4-carboxylic acid (0·5 g., recrystallised) was heated with a little cupric oxide. Decarboxylation began at 200° and the oxazole distilled at about 250° as a colourless oil. The chloroplatinate formed golden-yellow prisms, decomp. from 210° (Gabriel, *Ber.*, 1894, **27**, 218, records 218°). The *picrate* crystallised from ethanol in slender yellow needles, m. p. 145° (Found: C, 49·5; H, 3·2; N, 14·4. $C_{10}H_9ON,C_6H_3O_7N_3$ requires C, 49·9; H, 3·4; N, 14·7%).

2-Phenyl-5-methylglyoxaline-4-carboxylic acid (IV; R = CO_2H).—Ethyl 2-phenyl-5-methylglyoxaline-4-carboxylate (0·24 g.) was dissolved in potassium hydroxide solution (10 c.c. of 10%) by warming for ½ hour at 100°. The cooled solution was washed with ether and adjusted to pH 7. Fine needles of the *acid* (IV; R = CO_2H) (0·18 g.) separated on keeping. Recrystallisation from ethyl acetoacetate gave clusters of thin needles, m. p. 177° (decomp.) (Found: C, 64·9; H, 5·0. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 5·0%).

The acid (0·2 g.) was heated at 15 mm. pressure in a sublimation apparatus. Effervescence began at 160° and was complete at 180°. The sublimate was recrystallised from aqueous ethanol. The shiny needles of 2-phenyl-4-methylglyoxaline had m. p. 181—182° (John, *loc. cit.*, gave m. p. 181°). The product was sparingly soluble in benzene and almost insoluble in water (Found: C, 75·8; H, 6·4; N, 17·6. Calc. for $C_{10}H_{10}N_2$: C, 75·8; H, 6·3; N, 17·7%).

Synthesis of 2-Phenyl-4-methylglyoxaline.—(a) *From benzamidine and chloroacetone.* Benzamidine hydrochloride (6 g.) was dissolved in aqueous sodium hydroxide (20 c.c. of 5%), and the free base extracted with chloroform (45 c.c.). The dried ($CaCl_2$) solution was refluxed for 4 hours with chloroacetone (3 g.). On distillation 1 g. was obtained, b. p. 350°. Sublimation (160—180°/15 mm.) and recrystallisation

from aqueous ethanol gave the glyoxaline (0·7 g.); m. p. 181° undepressed on mixing with the material described in the preceding experiment.

(b) *From hippuric acid.* 2-Phenyl-4-(1-hydroxyethylidene)-4:5-dihydro-oxazol-5-one was prepared by the method of Elliott and Penny (*loc. cit.*), pyridine being used. The sodium salt of the oxazolone (5 g., prepared by evaporating a neutralised solution) was thoroughly mixed with potassium acetate (5 g.; this ingredient acts as a flux) and melted by heating and stirring over a free flame. When a test portion failed to give the characteristic colour with ferric chloride (about 3 minutes), the dark melt was cooled and dissolved in water. The combined solution from four such runs was boiled with a liberal quantity of charcoal. After filtration the solution was acidified, and the precipitated 2-phenyl-5-methyloxazole-4-carboxylic acid (III; R = CO_2H) collected and dried (12 g.). A portion recrystallised from benzene formed long slender needles, m. p. and mixed m. p. 180°. The acid (2 g.) was heated in a sealed tube with aqueous ammonia (10 c.c.; *d* 0·880) for 8 hours at 190°. The crude glyoxaline was collected and dried (1·5 g.). Sublimation and recrystallisation from aqueous ethanol gave 1·3 g., m. p. 181—182°, identical with the specimens prepared by methods described above.

Condensation of Benzimidomethyl Ether with Aminoacetone Hydrochloride.—The imido-ether (1·4 c.c.) was added to a solution of the hydrochloride (1 g.) in glacial acetic acid (4 c.c.) at 100°. The product was separated into neutral and basic fractions as already described. The aqueous acetic acid solution on addition of excess alkali gave a dark precipitate which was recrystallised (charcoal) from aqueous ethanol to give 2-phenyl-4-methylglyoxaline (0·37 g.), m. p. 180°, raised to 181—182° by sublimation in a vacuum and recrystallisation. The m. p. was not depressed by admixture with an authentic sample. The ethereal solution yielded no more glyoxaline on extraction with dilute hydrochloric acid. It was evaporated, and the residue boiled with 2N-sodium hydroxide. Extraction with ether then gave crude 2-phenyl-5-methyloxazole (0·3 g.), identified as the picrate, m. p. 144° alone or mixed with authentic material.

Condensation of Benzimidomethyl Ether with Aminoacetaldehyde Hydrochloride.—Carried out under the conditions of the foregoing experiment, this reaction gave a dark and tarry product. From the ethereal extract a trace of solid was obtained, which had m. p. 228—230° after recrystallisation from ethanol and was found to be 2:4:6-triphenyltriazine (Found: C, 81·7; H, 5·0; N, 13·4. Calc. for $C_{21}H_{15}N_3$: C, 81·5; H, 4·9; N, 13·6%).

Condensation of Heximidomethyl Ether with Ethyl α-Aminoacetoacetate Hydrochloride.—The imido-ether (1·2 c.c.) was dropped into a stirred solution of the hydrochloride (2 g.) in glacial acetic acid (4 c.c.) at 100°. The reaction mixture was worked up as described before. About 60% of the basic product was found in the diluted acetic acid solution, and the remainder was obtained by acid washings of the ether extract. Recrystallisation from benzene gave *ethyl 5-methyl-2-amylglyoxaline-4-carboxylate* (0·3 g.), m. p. 98—100°. Further crystallisation from light petroleum (b. p. 60—80°) gave long slender needles, m. p. 100—101° (Found: C, 64·3; H, 8·9. $C_{12}H_{20}O_2N_2$ requires C, 64·3; H, 8·9%).

The crude neutral product from the ether extract was hydrolysed by warming with sodium hydroxide (4 c.c. of 5%) for one hour on a steam-bath. After treatment with charcoal the cooled solution was washed well with ether and acidified to Congo-red. The precipitated oil solidified after a time. Recrystallisation from benzene gave *5-methyl-2-amyloxazole-4-carboxylic acid* (0·2 g.) in shiny broad plates, m. p. 108—109° raised to 110° by two crystallisations from methanol–light petroleum (Found: C, 61·1; H, 7·7; N, 7·0. $C_{10}H_{15}O_3N$ requires C, 60·9; H, 7·7; N, 7·1%).

Experiments on the Cyclisation of Ethyl 1-Ethoxyethylideneaminomalonate.—The ester (11 g.) on treatment with 1 equiv. of potassium ethoxide in alcohol–ether, gave the potassium enolate (6·4 g.). This was added gradually to boiling acetic acid (14 c.c.). The solution was poured into excess of cold potassium carbonate solution and extracted four times with ether. On removal of the ether the residue partly crystallised. Recrystallisation (once from benzene–light petroleum, once from ether) gave colourless polyhedra, m. p. 95—96°, of ethyl acetamidomalonate (Found: C, 50·1; H, 7·0; N, 6·4. Calc. for $C_5H_{11}O_3N$: C, 49·8; H, 6·9; N, 6·5%). The filtrate from the preparation of the potassium enolate was made acid to Congo-red with alcoholic hydrogen chloride. After a few days the solution was filtered and evaporated. The residue was distilled at 15 mm. up to a bath temperature of 150°. The distillate partly crystallised on keeping in the air. Recrystallisation from benzene–light petroleum gave the hydrate of ethyl mesoxalate in large colourless plates, m. p. 58—59° (Found: C, 44·0; H, 6·2; N, nil. Calc. for $C_5H_{12}O_6$: C, 43·8; H, 6·3%).

Ethyl 1-ethoxyethylideneaminomalonate (1 g.) was warmed with concentrated sulphuric acid (1 c.c.) to 120°. When effervescence ceased (10 minutes) the light yellow solution was poured into excess of potassium carbonate solution and extracted with ether. The evaporated extract gave a crystalline picrate with aqueous picric acid. Recrystallisation from alcohol gave small, fluffy, yellow needles (40 mg.), m. p. 147—148° (Found: C, 41·9; H, 4·5; N, 17·5. $C_5H_{11}N,C_6H_3O_7N_3$ requires C, 42·0; H, 4·5; N, 17·8%). This *picrate* was obtained in three separate experiments. The m. p. was sharply depressed by piperidine picrate, m. p. 148—149°. In another experiment the evaporated ethereal extract was distilled. The main fraction, b. p. 100—110° (bath)/0·05 mm., solidified and crystallised from ether to give ethyl aceturate, m. p. 44—46° (Found: C, 49·1; H, 7·7. Calc. for $C_6H_{11}O_3N$: C, 49·7; H, 7·7%).

Reaction of Benzimidomethyl Ether with Chloroacetone.—A mixture of the imido-ether (4·5 g.) and the ketone (3·2 g.) was refluxed (oil-bath) for 4 hours. The solution was freed from separated solid (identified as benzamide) and warmed with 2N-sodium hydroxide for ½ hour on the steam-bath. The oil was recovered (ether) and distilled; the fraction, b. p. 80—90°/15 mm., on redistillation gave 2-phenyl-4-methyloxazole (0·7 g.) (Found: C, 75·4; H, 6·2. Calc. for $C_{10}H_9ON$: C, 75·5; H, 5·7%). The chloroplatinate formed light yellow prisms, decomp. at 180° (Lewy, *Ber.*, 1888, **21**, 2193, recorded 170°). The *picrate* separated from aqueous ethanol in fine, light yellow needles, m. p. 143—144°, depressed to 140° when mixed with 2-phenyl-5-methyloxazole picrate (Found: N, 14·4. $C_{10}H_9ON,C_6H_3O_7N_3$ requires N, 14·4%).

Reaction of 2-Amyloxazole-4-carboxylic Acid with Ammonia.—The acid (1·83 g.; 0·01 mole) was heated in a sealed tube with aqueous ammonia (15 c.c.; *d* 0·880) for one hour at 140° and then one hour

at 150°. After removal of most of the ammonia the liquid was extracted with chloroform. The product was distilled (mostly at 275—280°). The higher fractions smelled strongly of amyl cyanide, doubtless from pyrolysis of some by-product. The distillate was converted in good yield into the picrolonate of 2-amylglyoxaline, m. p. 189·5—190·5° from acetone (cf. Cornforth *et al.*, "The Chemistry of Penicillin," Chap. XXI). The aqueous ammoniacal liquor gave no unchanged acid on acidification.

2-Amyloxazole (1·39 g.; 0·01 mole) was heated with ammonia (15 c.c.) under precisely the same conditions as for the acid. On working up, the oxazole was recovered unchanged; there was no indication that any glyoxaline had been formed.

Our thanks are due to the British Council for enabling one of us to take part in this work.

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NATIONAL INSTITUTE FOR MEDICAL RESEARCH, HAMPSTEAD. [*Received, December 28th*, 1947.]

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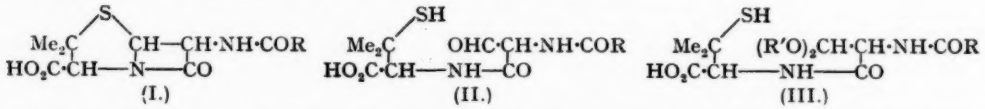
399. *Experiments on a Synthesis of Penicillin.*

By J. W. CORNFORTH and H. T. HUANG.

Various attempts are described to prepare *N*-(*n*-amylpenaldyl)penicillamine (II; R = *n*-C_5H_{11}). A novel oxazole synthesis incidental to this work is described.

AMONG the many schemes for synthesis of penicillins (I) there are some which involve intramolecular removal of water in the final stage. The possibility of dehydrating various penicilloic acid derivatives has been tried exhaustively and has led to no significant amount of antibiotic. Alternative intermediates are the *N*-penaldylpenicillamines (II), and this paper gives an account of some attempts to synthesise them.



(I.) (II.) (III.)

Acetals of (II) (III; R = CH_2Ph, R′ = Me or Et) were prepared independently by several groups (Merck and Co.; University of Michigan; Squibb Institute; see "The Chemistry of Penicillin"); in all cases the azide of the appropriate penaldic acid acetal was condensed with penicillamine to give (III). Pyrolysis of (III; R = CH_2Ph, R′ = Me) was reported (Squibb Institute, *loc. cit.*) to give slight antibiotic activity but the result does not seem to be readily reproducible. Because others were engaged on this line, and because the acid hydrolysis of (III) to (II) seemed likely to be difficult, we explored other routes.

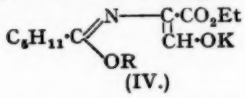
A synthesis of oxazoles by the action of acids on potassium enolates of the structure (IV) has been described (Cornforth and Cornforth, *J.*, 1947, 96). A theory of the mechanism of this change (Cornforth and Huang, this vol., p. 1960) led to the idea that in presence of alcohol a 5-ethoxyoxazoline (V; X = OEt) might be formed. If the carbethoxyl group in (V) could be modified to form a hydrazide, an azide, and finally an *N*-acylpenicillamine, it was expected that the final hydrolysis to (II) would be facile.

Potassium ethyl α-(1-ethoxyhexylideneamino)-β-hydroxyacrylate (IV; R = Et) on treatment with hydrogen chloride in ethanol gave a low-melting solid in good yield; this, however, was not the oxazoline but the diethyl acetal of ethyl *n*-amylpenaldate (VI; X = OEt; Chas. Pfizer and Co., "The Chemistry of Penicillin"). The structure was established by conversion into the 2 : 4-dinitrophenylhydrazone of ethyl *n*-amylpenaldate and by alkaline hydrolysis to *n*-amylpenaldic acid diethyl acetal (Cook, Elvidge, and Heilbron, "The Chemistry of Penicillin"; Chas. Pfizer and Co., *op. cit.*). Condensation of heximidomethyl ether with glycine ethyl ester hydrochloride gave *ethyl 1-methoxyhexylideneaminoacetate*, which was formylated to *potassium ethyl* α-(1-*methoxyhexylideneamino*)-β-*hydroxyacrylate* (IV; R = Me); the latter also gave (VI; X = OEt) with ethanolic hydrogen chloride. An attempt to obtain (V; X = OEt) by using less ethanol in the reaction with (IV; R = Et) only resulted in the formation of much ethyl 2-*n*-amyloxazole-4-carboxylate.

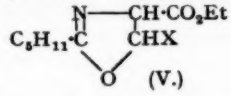
The ester (VI; X = OEt) being thus available, it was converted into the corresponding *hydrazide* and thence into the azide. Reaction of the latter with D-penicillamine gave the amorphous N-(α-*hexamido*-ββ-*diethoxypropionyl*)-D-*penicillamine* (III; R = *n*-C_6H_{11}, R′ = Et). Pyrolysis of this substance failed to give antibiotic activity.

The reaction of (IV; R = Et) with ethylthiol and dry hydrogen chloride was now studied. The product, obtained by distillation in satisfactory yield, was not the penaldic ester thioacetal (VI; X = SEt) but had the composition of the 5-ethylthio-oxazoline (V; X = SEt). The

corresponding acid was obtained on alkaline hydrolysis. The strong selective absorption of these two substances at 2800 A. left no doubt, however, that they were *ethyl α-hexamido-β-ethylthioacrylate* and the corresponding *acid* (VII; R = Et), respectively.



(IV.)



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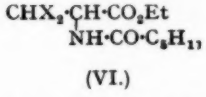
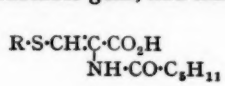


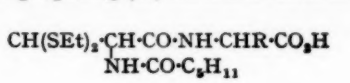
(VI.)

Ethyl α-hexamido-ββ-diethylthiopropionate (VI; X = SEt) was readily prepared from the unsaturated ester and ethylthiol by addition of a little sodium. The ester (VI; X = SEt) could be hydrolysed by alkali, but on acidification ethylthiol was lost, and the acid (VII; R = Et) formed. This accords with Posner's observations (*Ber.*, 1899, **32**, 2865; 1901, **34**, 2643) on the thioacetals of acetoacetic ester.

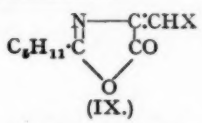
The use of mercuric chloride to regenerate carbonyl compounds from their thioacetals has produced good results in the acyclic sugar series (Levene and Meyer, *J. Biol. Chem.*, 1926, **69**, 175; Wolfrom, *J. Amer. Chem. Soc.*, 1929, **51**, 2188). The ester (VI; X = SEt) was cleaved by mercuric chloride–cadmium carbonate in aqueous acetone, ethyl *n*-amylpenaldate being isolated as the 2 : 4-dinitrophenylhydrazone. Under the same conditions the ethyl ester of (VII; R = Et) was recovered unchanged. Following this lead, we converted the ester (VI; X = SEt) by way of the *hydrazide* into the azide. The latter could be condensed with glycine to give N-(*α-hexamido-ββ-diethylthiopropionyl*)*glycine* (VIII; R = H) and with DL-α-amino-β-methoxy*iso*valeric acid to *α-(α-hexamido-ββ-diethylthiopropionamido)-β-methoxyisovaleric acid* (VIII; R = CMe_2·OMe); but with D- or DL-penicillamine the acidic product was a trace of intractable gum, and this way of preparing (II) *via* a thioacetal had to be abandoned.



(VII.)



(VIII.)

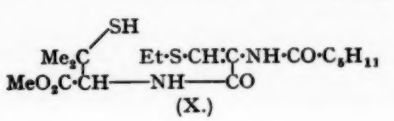


(IX.)

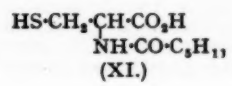
When the salt (IV; R = Et) was treated with benzylthiol and hydrogen chloride, a crystalline product could be obtained without distillation. The analysis and ultra-violet absorption spectrum indicated that this was *ethyl α-hexamido-β-benzylthioacrylate*. Alkaline hydrolysis gave the corresponding *acid* (VII; R = CH_2Ph).

The results outlined above are consistent with the view that an oxazoline of type (V) is the primary product when a salt such as (IV) reacts with hydrogen chloride in the presence of an alcohol or thiol. The oxazoline can undergo prototropic change to give an α-acylamidoacrylic ester, as with the thiols; when ethanol is used further reaction can take place, either before or after the prototropic change, to give a penaldic acetal of type (VI; X = OEt).

Availability of the acid (VII; R = Et) suggested a new line of attack. On treatment with acetic anhydride (less well with phosphorus pentachloride), the acid was smoothly dehydrated to *5-keto-2-n-amyl-4-ethylthiomethylene-4 : 5-dihydro-oxazole* (IX; X = SEt). Wellcome Institute workers ("The Chemistry of Penicillin," Chap. XXI) have shown that in alkylthiomethylene-oxazolones the 5-keto-group is usually the most reactive electrophilic centre; and here was no exception, for the oxazolone (IX; X = SEt) was decomposed by alkali to the parent acid (VII; R = Et), and by benzylamine and *p*-toluidine to the *benzylamide* and *p-toluidide* of this acid. Condensation with glycine ethyl ester was also achieved; it was found expedient to hydrolyse with alkali and isolate N-(*α-hexamido-β-ethylthioacrylyl*)*glycine*. With D-penicillamine methyl ester the usual difficulty was encountered and prolonged refluxing of the ester with the oxazolone (IX; X = SEt) in dry ether was the only procedure which furnished, in very low yield, a crystalline product. The ultra-violet absorption showed this to be N-(*α-hexamido-β-ethylthioacrylyl*)-D-*penicillamine methyl ester* (X). The preparation of (X) required a considerable quantity of the oxazolone (IX; X = SEt) and this was prepared by treatment of 5-keto-2-amyl-4-methoxymethylene-4 : 5-dihydro-oxazole (IX; X = OMe) with ethylthiol in pyridine (for preparation of the methoxymethyleneoxazolone, see Cornforth *et al.*, "The Chemistry of Penicillin," Chap. XXI). No success has yet attended our efforts to add ethylthiol to (X), or to induce intramolecular addition of the thiol group to the double bond.



(X.)

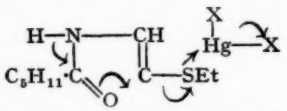
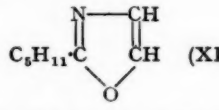


(XI.)

The benzylthio-acid (VII; R = CH_2Ph) readily yielded *5-keto-2-n-amyl-4-benzylthiomethylene-4 : 5-dihydro-oxazole* (IX; X = $S{\cdot}CH_2Ph$) with acetic anhydride. The oxazolone behaved like its ethylthio-analogue : the ring was opened by alkali and by benzylamine to give the acid (VII; R = CH_2Ph) and its *benzylamide* respectively. It was noted that 5-keto-2-phenyl-4-benzylthiomethylene-4 : 5-dihydro-oxazole on similar treatment with benzylamine gave the *benzylamide* of α-benzamido-β-benzylthioacrylic acid; this is in contrast to the behaviour of the same oxazolone with aniline, which converts it into the anilinomethyleneoxazolone (Barber, Sack, and Stickings, " The Chemistry of Penicillin," Chap. XXI.

It was hoped that a compound of type (X) would be available from (IX; X = $S{\cdot}CH_2Ph$) and penicillamine methyl ester, when removal of the benzyl group with sodium and liquid ammonia might give the thioaldehyde corresponding to (II). A model reduction of the acid (VII; R = CH_2Ph) showed, however, that the double bond was also saturated, DL-N-*hexoylcysteine* (XI) being the only crystalline product isolated : and, as the condensation of the oxazolone with penicillamine methyl ester would give only gummy material, the work was abandoned at this point.

When mercuric chloride was added to a neutralised aqueous solution of α-hexamido-β-ethylthioacrylic acid (or its benzylthio-analogue) carbon dioxide was evolved, and on boiling, the characteristic smell of 2-amyloxazole (XII) appeared. The oxazole was isolated in poor yield as the picrate. In order to examine the mechanism of this change, β-ethylthiocrotonic acid, $CH_3{\cdot}C(SEt){:}CH{\cdot}CO_2H$ (Posner *loc. cit.*), was treated with mercuric chloride under similar conditions. The products were carbon dioxide, acetone, and ethylthiomercuric chloride; no methylacetylene could be detected. This result makes it unlikely that (XII) is formed *via* the acetylene $C_5H_{11}{\cdot}CO{\cdot}NH{\cdot}C{:}CH$, and a more likely mechanism is that of nucleophilic attack by the amide oxygen atom [in the intermediate complex (XIII)] upon the carbon atom bearing the alkylthio-group, removal of which is facilitated by the mercury.

(XIII.)  →  (XII.)

β-*Ethylthiopropionic acid* was also treated with mercuric chloride; in this case no carbon dioxide was liberated.

Experimental.

Ethyl 1-*Methoxyhexylideneaminoacetate*.—Heximidomethyl ether was prepared in 55% yield by keeping equimolecular amounts of *n*-amyl cyanide, methanol, and hydrogen chloride in dry ether for three days at 0°. The crystalline hydrochloride was washed with ether and decomposed by aqueous potassium carbonate and ether, and the product distilled. A mixture of the imidoether (21 g.) and ether (20 c.c.) was shaken with a solution of glycine ethyl ester hydrochloride (24 g.) in water (20 c.c.) for one hour. The ethereal layer, after being washed with water, was dried and distilled, giving *ethyl α-methoxyhexylideneaminoacetate* (15 g.), a colourless oil, b. p. 85—90°/0·1 mm. (Found : C, 61·2; H, 9·6. $C_{11}H_{21}O_3N$ requires C, 61·4; H, 9·8%).

Potassium Ethyl α-(1-Methoxyhexylideneamino)-β-hydroxyacrylate (IV; R = Me).—Potassium (1·7 g.) was dissolved in a mixture of ethanol (6 c.c.) and ether (20 c.c.) under gentle reflux; the solution was diluted to 250 c.c. with ether. A cold mixture of the foregoing ester (10 g.) and ethyl formate (5 g.) was added at −5°, and this temperature then maintained for two hours. After being kept at 0° overnight, the pale pink *potassium* salt (10 g.) was collected and washed with ether; the filtrate and washings afforded an additional 1 g. after keeping for a day. The product was crystalline and deliquescent : it gave the characteristic ferric chloride test (Cornforth and Cornforth, *J.*, 1947, 101) (Found : N, 5·0. $C_{12}H_{20}O_4NK$ requires N, 5·0%). The same conditions were applied to prepare the ethoxy-analogue (IV; R = Et) in similar yield.

Action of Ethanol and Hydrogen Chloride on the Salt (IV; R = Et).—Potassium α-(1-ethoxyhexylideneamino)-β-hydroxyacrylate (15 g.) was added during 10 minutes to a stirred solution of hydrogen chloride (15 g.) in dry ethanol (150 c.c.) at −15°. After 2½ hours' stirring, the mixture was allowed to come slowly to room temperature and left overnight; the alcohol was removed at low pressure, and the remaining thick oil neutralised with cold aqueous potassium carbonate under ether. After three more extractions with ether the combined extract was dried and distilled, giving ethyl *n*-amylpenaldate diethyl acetyl (9 g.), b. p. 125°/0·1 mm., which solidified on cooling and had m. p. 50° after two recrystallisations from ethanol (Chas. Pfizer and Co., *op. cit.*, record m. p. 51°) (Found : C, 59·7; H, 9·5; N, 5·0. Calc. for $C_{15}H_{29}O_5N$: C, 59·4; H, 9·6; N, 4·6%). When this experiment was carried out in ether and with only 1½ equivs. of ethanol the main fraction had b. p. 95—100°/0·1 mm. and on saponification gave 2-amyloxazole-4-carboxylic acid, m. p. 94° undepressed by authentic material (Found : C, 58·8; H, 7·0. Calc. for $C_9H_{13}O_3N$: C, 58·9; H, 7·1%).

n-*Amylpenaldic Acid Diethylacetal* (VI; X = OEt).—Hydrolysis of the above ethyl ester acetal (2N-sodium hydroxide or 5% aqueous-alcoholic potassium hydroxide) gave the acid, slender needles, m. p. 80° (Found : OEt, 28·2; equiv., 302. Calc. for $C_{13}H_{25}O_5N,1{\cdot}5H_2O$: OEt, 29·8%; equiv., 302). Other workers (*locc. cit.*) have recorded varying degrees of hydration. The anhydrous acid was obtained

by prolonged drying over phosphoric oxide in a vacuum, and recrystallised from light petroleum (b. p. 60—80°); m. p. 60—61° (Found: C, 56·5; H, 9·2. Calc. for $C_{13}H_{25}O_5N$: C, 56·7; H, 9·1%).

α-Hexamido-ββ-diethoxypropionylhydrazide.—Ethyl amylpenaldate diethyl acetal (2 g.) and hydrazine hydrate (2 c.c. of 50%) were treated with enough alcohol to effect mutual solution, and the mixture warmed for two hours at 60°, cooled, triturated and the solid collected. Two recrystallisations from aqueous ethanol gave the *hydrazide* (2 g.) in clusters of long silky needles, m. p. 161° (Found: C, 53·8; H, 9·2; N, 14·3. $C_{13}H_{27}O_4N_3$ requires C, 53·9; H, 9·3; N, 14·5%). The *benzylidene* derivative was prepared by adding benzaldehyde to an acid solution of the hydrazide; it separated from alcohol in long thin needles, m. p. 168·5° (Found: C, 63·7; H, 8·4; N, 11·1. $C_{20}H_{31}O_4N_3$ requires C, 63·7; H, 8·2; N, 11·1%).

N-(*α-Hexamido-ββ-diethoxypropionyl*)-D-*penicillamine* (III; R = *n*-C_5H_{11}; R′ = Et).—A solution of the above hydrazide (290 mg.) in N-hydrochloric acid (4 c.c.) at 0° was treated with a similarly cooled solution of sodium nitrite (90 mg.) in water (1 c.c.) with vigorous stirring. The thick oily drops of azide solidified on prolonged rubbing. The crude azide was collected, washed with a little cold water, and added at once to a solution of D-penicillamine hydrochloride (190 mg.) and anhydrous sodium carbonate (200 mg.) in water (3 c.c.) under carbon dioxide. The mixture was stirred for one hour then shaken vigorously for six hours, filtered, and the filtrate washed with ether, cooled to 0°, and brought to pH 4. The precipitated gum was collected by ether extraction and obtained as a white powder. It was purified by reprecipitation from aqueous sodium carbonate. The N-*acylpenicillamine* (200 mg.) was soluble in all common organic solvents and showed no tendency to crystallise. Its alkaline solution gave an intense red colour with sodium nitroprusside (Found: C, 53·5; H, 8·1; S, 7·7. $C_{18}H_{34}O_6N_2S$ requires C, 53·2; H, 8·4; S, 7·9%); $[\alpha]_D^{20°}$ +9·1° (*c* = 6 in ethanol). Pyrolysis of 5 mg. specimens was tried (*a*) at 120° for 10 minutes, then 150° for 10 minutes; (*b*) at 150° for 15 minutes. The pyrolysates after being taken into phosphate buffer showed no significant antibiotic activity against *S. aureus*.

Action of Ethylthiol and Hydrogen Chloride on the Salt (IV; R = Et).—Hydrogen chloride (15 g.) was passed during 20 minutes into a stirred suspension of potassium ethyl α-(α′-ethoxyhexylideneamino)-β-hydroxyacrylate (10 g.) in ether (100 c.c.) and ethylthiol (2·6 g.) at −5° under stringently anhydrous conditions. After 3 days (room temp.) the mixture was evaporated at low pressure, and the residual oil neutralised under ether with cold saturated aqueous potassium carbonate. Distillation of the ethereal extract gave a fraction (1 g.) boiling below 100°/14 mm., which was discarded; then a fraction (2 g.), b. p. 90—120°/0·1 mm., which gave 2-amyloxazole-4-carboxylic acid (m. p. and mixed m. p. 94°) on saponification. The main product (4·5 g.) boiled at 155—160°/0·1 mm. *Ethyl α-hexamido-β-ethylthioacrylate* was an oil, $n_D^{20°}$ 1·5149 (Found: C, 57·0; H, 8·6; N, 5·3; S, 11·7. $C_{13}H_{23}O_3NS$ requires C, 57·1; H, 8·4; N, 5·1; S, 11·7%). The absorption spectrum (in methanol) was taken on a freshly prepared, twice redistilled sample. There was a maximum at 2850 A. (ε, 10,620) and a minimum at 2440 A.

α-Hexamido-β-ethylthioacrylic Acid (VII; R = Et).—The foregoing ester (2 g.) was warmed with sodium hydroxide (20 c.c. of N) at 60° for 6 hours. The solution was washed with ether and acidified with N-hydrochloric acid. The *acid* (1·5 g.) was collected and dried in a vacuum over sodium hydroxide. Repeated crystallisation from benzene–light petroleum gave long, thin needles, m. p. 108° (Found: C, 53·6; H, 7·7; N, 5·7; S, 13·0. $C_{11}H_{19}O_3NS$ requires C, 53·8; H, 7·7; N, 5·7; S, 13·1%); λ max. 2800 A. (ε, 12,250); λ min. 2420 A. (in methanol).

Ethyl α-Hexamido-ββ-diethylthiopropionate (VI; X = SEt).—A small piece of freshly cut sodium was added to a solution of ethyl α-hexamido-β-ethylthioacrylate (2·5 g.) in ethylthiol (2·5 c.c.). After four days dry ether was added, and the solution filtered and evaporated. A solution of the residue in light petroleum (b. p. 60—80°) crystallised on evaporation at low pressure, giving the *diethylthioacetal* (2·5 g.) in long white needles, m. p. 40—45° raised to 50—51° after three recrystallisations from light petroleum (Found: C, 53·8; H, 8·7; N, 4·2; S, 18·0. $C_{15}H_{29}O_3NS_2$ requires C, 53·7; H, 8·7; N, 4·2; S, 19·1%). An attempt to prepare this substance from ethyl *n*-amylpenaldate with ethylthiol and hydrogen chloride led to an intractable product. When the diethylthioacetal ester (0·2 g.) was dissolved (½ hour at 100°) in N-sodium hydroxide (2 c.c.) and the solution was washed with ether and acidified to Congo-red, a strong odour of ethylthiol was noted and α-hexamido-β-ethylthioacrylic acid was precipitated (0·1 g.), m. p. and mixed m. p. 108° after recrystallisation from light petroleum (b. p. 60—80°).

Cleavage of Ethyl α-Hexamido-ββ-diethylthiopropionate with Mercuric Chloride.—A mixture of the thioacetal ester (180 mg.), mercuric chloride (360 mg.), cadmium carbonate (480 mg.), acetone (3 c.c.), and water (1·5 c.c.) was shaken mechanically for 24 hours. The precipitate was separated and washed with acetone and water. The filtrate, which gave a purple colour with alcoholic ferric chloride, was evaporated in the presence of a little cadmium carbonate, and the residue extracted with chloroform. Evaporation of the chloroform left an oil which was treated with an excess of 2 : 4-dinitrophenylhydrazine in 5N-hydrochloric acid. After 12 hours the yellow precipitate, m. p. 150°, was collected and recrystallised twice from ethanol and twice from ethyl acetate; final m. p. 166°, undepressed on admixture with authentic ethyl *n*-amylpenaldate 2 : 4-dinitrophenylhydrazone, m. p. 166—167°.

α-Hexamido-ββ-diethylthiopropionylhydrazide.—The thioacetal ester (VI; X = SEt) (1·8 g.) was warmed at 50° for 1 hour with hydrazine hydrate (0·8 c.c. of 50%) and ethanol (5 c.c.). Next day an equal volume of water was added. On very slow cooling of the warmed solution the *hydrazide* (1·6 g.) separated; soft silky needles, m. p. 148—149° unaffected by further crystallisation (Found: C, 48·7; H, 8·2; N, 13·4. $C_{13}H_{27}O_2N_3S_2$ requires C, 48·6; H, 8·4; N, 13·1%). The *benzylidene* derivative was prepared by shaking a solution in N-hydrochloric acid with benzaldehyde; slender needles from ethanol, m. p. 163° (Found: C, 58·5; H, 7·4. $C_{20}H_{31}O_2N_3S_2$ requires C, 58·7; H, 7·6%).

N-(*α-Hexamido-ββ-diethylthiopropionyl*)*glycine* (VIII; R = H).—An ice-chilled solution of sodium nitrite (43 mg.) in water (0·2 c.c.) was added to a stirred, similarly cooled solution of the above hydrazide (200 mg.) in N-hydrochloric acid (3 c.c.). The gummy azide was extracted with ether and obtained as an amorphous powder on evaporation. This was stirred with a solution of glycine (47 mg.) and potassium carbonate (88 mg.) in water (2 c.c.) for two hours. Next day the solution was filtered, and the filtrate

washed with ether, cooled, and acidified to Congo-red with 2N-hydrochloric acid. The *acylglycine* (44 mg., m. p. 145°) separated from aqueous ethanol in minute needles, m. p. 153° (Found: C, 48·6; H, 8·0; N, 7·7. $C_{15}H_{28}O_4N_2S_2,0{\cdot}5H_2O$ requires C, 48·3; H, 7·8; N, 7·5%).

α-(α-Hexamido-ββ-diethylthiopropionamido)-β-methoxyisovaleric Acid (VIII; R = CMe_2·OMe).—On repetition of the above experiment, using DL-α-amino-β-methoxy*iso*valeric acid (152 mg.) in place of glycine, the *acid* (VIII; R = CMe_2·OMe) was obtained (45 mg.); it crystallised from aqueous ethanol in microscopic rods, m. p. 118—120°, which were dried in a vacuum over sodium hydroxide (Found: C, 51·3; H, 8·0. $C_{19}H_{36}O_5N_2S_2,0{\cdot}5H_2O$ requires C, 51·2; H, 8·3%).

When the same conditions were applied in an attempt to condense the azide with D-penicillamine, a very low yield of yellow gum was obtained. When the reaction was carried out in homogeneous solution (aqueous dioxan), or by shaking the penicillamine solution with an ethereal solution of the azide, the result was no better.

Action of Benzylthiol and Hydrogen Chloride on the Salt (IV; R = Et).—Dry hydrogen chloride (20 g.) was passed during 20 minutes into a suspension of potassium ethyl α-(1-ethoxyhexylideneamino)-β-hydroxyacrylate (10 g.) in ether (100 c.c.) and benzylthiol (5·1 c.c.). The mixture was shaken frequently and kept at 0°. After two days at room temperature it was evaporated, and the residue washed with concentrated potassium carbonate solution and extracted with ether. The oil remaining after removal of the ether crystallised on being rubbed with light petroleum (b. p. 40—60°; 50 c.c.). The crude *ethyl α-hexamido-β-benzylthioacrylate* (5·52 g.; m. p. 65—75°; further 3·4 g. from mother-liquors) was recrystallised from light petroleum, b. p. 60—80°; clusters of fine needles, m. p. 77° (Found: C, 65·0; H, 7·5; N, 4·5; S, 9·6. $C_{18}H_{25}O_3NS$ requires C, 64·5; H, 7·5; N, 4·2; S, 9·6%). The ultra-violet absorption curve of a methanol solution showed a maximum at 2840 A. (ε, 18,000) and a minimum at 2460 A. The substance was unaffected by keeping with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid for three days.

α-Hexamido-β-benzylthioacrylic Acid (VII; R = CH_2Ph).—The crude ester (3 g.) was refluxed for 20 minutes with sodium hydroxide (30 c.c. of 2N). After being washed with ether, the solution was acidified (Congo-red), and the *acid* (2·1 g.) collected. Two recrystallisations from benzene gave long, thin needles, m. p. 161—161·5° (Found: C, 62·2; H, 6·6; N, 4·5; S, 10·0. $C_{16}H_{21}O_3NS$ requires C, 62·5; H, 6·9; N, 4·6; S, 10·4%); λ max. 2840 A. (ε, 13,500); λ min. 2440 A. (in methanol).

5-Keto-2-n-amyl-4-ethylthiomethylene-4 : 5-dihydro-oxazole (IX; X = SEt).—Ethylthiol (3·5 g.) was added to a solution of 5-keto-2-*n*-amyl-4-methoxymethylene-4 : 5-dihydro-oxazole (11 g.) in pyridine (40 c.c.). After 24 hours the pyridine was removed in a vacuum, and the residue distilled. The crude, pale yellow oxazolone, b. p. 100—110°/0·05 mm., was immediately warmed with 2N-sodium hydroxide until all was in solution. After working up in the usual manner, α-hexamido-β-ethylthioacrylic acid (10 g.) was collected. Two recrystallisations from benzene gave shining needles (8 g.), m. p. 108°.

The acid (4 g.) was dissolved in acetic anhydride (20 c.c.). After 20 minutes at 100° distillation at low pressure gave the *oxazolone* (IX; X = SEt) as a light yellow oil, b. p. 100—110°/0·05 mm. (3·6 g.); $n_D^{20°}$ 1·5510 (Found: C, 58·6; H, 7·6; N, 6·4; S, 14·3. $C_{11}H_{17}O_2NS$ requires C, 58·2; H, 7·5; N, 6·2; S, 14·1%). The dehydration could also be effected by warming the acid (0·45 g.) with phosphorus pentachloride (0·4 g.) in chloroform (2 c.c.). On distillation, decomposition (of a hydrochloride?) took place at 120°/0·1 mm. and the oxazolone (0·2 g.) distilled (Found: C, 58·6; H, 7·9%). Alkaline hydrolysis gave the acid (VII; R = Et).

Reaction of the Oxazolone (IX; X = SEt) *with Amines*.—(i) Benzylamine (2 drops) was added to a solution of the oxazolone (25 mg.) in dry ether (3 c.c.). After one hour at 0° the crystalline *α-hexamido-β-ethylthioacrylylbenzylamide* was collected and recrystallised from acetone–ether; m. p. 127—128° (Found: C, 64·1; H, 7·6; S, 9·1. $C_{18}H_{26}O_2N_2S$ requires C, 64·6; H, 7·8; S, 9·6%). (ii) The oxazolone was similarly treated with *p*-toluidine and left overnight. *α-Hexamido-β-ethylthioacrylyl-p-toluidide* formed tiny prisms, m. p. 104°, from acetone–ether (Found: C, 64·2; H, 7·7; S, 9·6. $C_{18}H_{26}O_2N_2S$ requires C, 64·6; H, 7·8; S, 9·6%). (iii) A mixture of the oxazolone (1·6 g.), glycine ethyl ester (0·8 g.), and pure dry ether (20 c.c.) was refluxed gently for 12 hours. After evaporation at low pressure the product was warmed with sodium hydroxide (20 c.c. of N) for 20 minutes, and the resulting solution, after being washed with ether, was acidified (Congo-red). After three days the partly crystalline product was collected and washed with ether. Recrystallisation thrice from benzene–ethanol (charcoal) gave shiny rhombs of *N-(α-hexamido-β-ethylthioacrylyl)glycine*, m. p. 160° (Found: C, 51·7; H, 7·4; N, 9·4. $C_{13}H_{22}O_4N_2S$ requires C, 51·7; H, 7·3; N, 9·3%). (iv) A mixture of the oxazolone (3·1 g.), D-penicillamine methyl ester (2·23 g.), and pure dry ether (50 c.c.) was refluxed for 20 hours, then set aside for half a day. An equal volume of light petroleum (b. p. 40—60°) was added, and the mixture kept at −30° for two hours. After centrifuging and washing twice with ether–light petroleum (1 : 1) the solid, which now appeared free from gum, was collected by means of dry ether; m. p. 128—129°, yield 200 mg. Recrystallisation from benzene–light petroleum (b. p. 40—50°) gave the *N-(α-hexamido-β-ethylthioacrylyl)-D-penicillamine* (X) in fine thin needles, m. p. 129° (Found: C, 52·3; H, 7·6; N, 7·1; S, 16·4. $C_{17}H_{30}O_4N_2S_2$ requires C, 52·3; H, 7·7; N, 7·2; S, 16·4%). The nitroprusside test for sulphydryl was negative, but a positive Feigl azide–iodine reaction was observed. The ultra-violet absorption curve showed a maximum at 2840 A. (ε, 16,000) and a minimum at 2430 A. (in methanol). From the mother-liquor an amorphous powder of the same composition could be separated (200 mg.); this softened and melted between 70° and 90°. The above procedure was the only one found to give crystalline material.

5-Keto-2-n-amyl-4-benzylthiomethylene-4 : 5-dihydro-oxazole (IX; X = S·CH_2Ph).—A mixture of benzylthiol (1·1 c.c.), 5-keto-2-*n*-amyl-4-methoxymethylene-4 : 5-dihydro-oxazole (1·7 g.), and pyridine (5 c.c.) was kept at room temperature and 20 mm. pressure (to remove methanol) for 8 hours; the pyridine was then removed over sulphuric acid in a vacuum. After being kept for 10 hours at 0° the viscous oil solidified and was recrystallised from ether–light petroleum (b. p. 40—60°). The *oxazolone* formed microscopic silky needles, m. p. 65—66° (Found: C, 66·5; H, 6·7; S, 11·4. $C_{14}H_{15}O_2NS$ requires C, 66·4; H, 6·6; S, 11·1%). The product was converted smoothly by aqueous alkali into the expected α-hexamido-β-benzylthioacrylic acid, m. p. and mixed m. p. 161·5°. When the oxazolone

(50 mg.) was kept for 18 hours with benzylamine (4 drops) in dry ether (5 c.c.), *α-hexamido-β-benzylthioacrylylbenzylamide* (40 mg.) separated in soft fibrous needles, m. p. 129—130° unaffected by recrystallisation from acetone–ether (Found: C, 69·2; H, 7·0. $C_{23}H_{28}O_3N_2S$ requires C, 69·6; H, 7·1%). In a similar manner *α-benzamido-β-benzylthioacrylylbenzylamide* was obtained from 5-keto-2-phenyl-4-benzylthiomethylene-4 : 5-dihydro-oxazole (m. p. 122—124°) and benzylamine in dry ether; the amide separated from acetone–ether in fine aggregated needles, m. p. 227° (Found: C, 71·2; H, 5·4. $C_{24}H_{23}O_2N_2S$ requires C, 71·6; H, 5·5%).

Action of Sodium in Liquid Ammonia on α-Hexamido-β-benzylthioacrylic Acid.—Sodium (0·35 g. required) was added in slices to a stirred solution of the acid (1·4 g.) in liquid ammonia (20 c.c.) until a permanent blue colour appeared. A little ammonium chloride was added, and the ammonia evaporated. An aqueous solution of the residue was washed with ether, acidified, and extracted with ether. The extract after treatment with charcoal was evaporated; the residual oil crystallised on trituration with light petroleum. The solid (0·1 g.) after two recrystallisations from benzene–light petroleum (b. p. 40—60°) gave DL-*N-hexoylcysteine*, long slender needles, m. p. 131—132°. The nitroprusside test was positive (Found: C, 49·2; H, 7·7; S, 14·2. $C_9H_{17}O_3NS$ requires C, 49·3; H, 7·8; S, 14·6%).

Action of Mercuric Chloride on α-Hexamido-β-ethylthioacrylic Acid.—To a neutral solution of the acid (1 g.) in 0·1N-sodium hydroxide, mercuric chloride (1·11 g.) was added, and the resulting suspension refluxed for one hour: evolution of carbon dioxide was complete in 10 minutes. Water (10 c.c.) was added, and the mixture distilled. The distillate was made alkaline and extracted with ether, which was then washed thrice with 5% sodium hydroxide, dried ($CaSO_4$) and evaporated. The residual 2-amyloxazole was converted into the picrate, m. p. and mixed m. p. 85° after crystallisation from ethanol.

Action of Mercuric Chloride on β-Ethylthiocrotonic Acid.—Mercuric chloride (0·93 g.) was added to a neutral solution of the acid (0·5 g.; m. p. 92°) in 0·1N-sodium hydroxide. The mixture was warmed to 60°; a stream of carbon dioxide-free air after passing through it was led through aqueous barium hydroxide, an acetylene test solution (Ilosvay, *Ber.*, 1899, **32**, 2698), and finally a solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. Carbon dioxide and acetone (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 125°) were thus detected, but no methylacetylene. The reaction was completed by warming on a steam-bath, and the crystalline residual precipitate collected. This consisted of ethylthiomercuric chloride (Found: C, 8·1; H, 1·7. Calc. for C_3H_5ClSHg: C, 8·1; H, 1·7%).

β-Ethylthiopropionic Acid.—Sodium (4·25 g.) was added in slices to a solution of β-chloropropionic acid (10 g.) and ethylthiol (5·15 g.) in ethanol (20 c.c.). After refluxing for one hour, the acidic products were isolated by means of ether and fractionally distilled. β-Ethoxypropionic acid was thereby separated from the required *acid*, which had b. p. 135°/15 mm., $n_D^{20°}$ 1·4832 (Found: C, 45·1; H, 7·8; S, 23·5. $C_5H_{10}O_3S$ requires C, 44·7; H, 7·5; S, 23·9%).

We wish to thank Sir Robert Robinson, P.R.S., for his interest in this work, and the British Council for enabling one of us to take part in it.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, December 28th*, 1947.]

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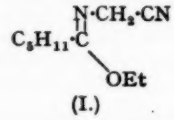
400. *Synthesis of a 4-Cyano-oxazole.*

By J. W. CORNFORTH and H. T. HUANG.

The preparation of 4-*cyano*-2-n-*amyloxazole* is described, together with some curious reactions of an intermediate (II).

THE extension of a method previously described (*J.*, 1947, 96) to the preparation of 4-cyano-oxazoles has been achieved without complications. Heximidoethyl ether with the hydrochloride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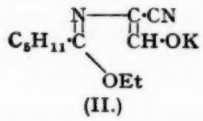
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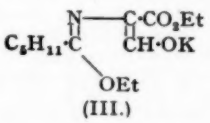
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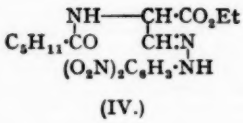
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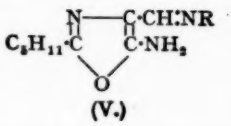
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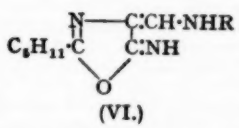
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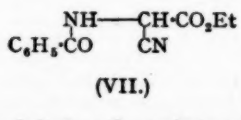
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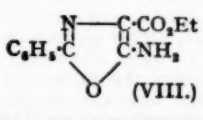
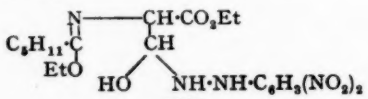

(VIII.)

or hydrogen sulphate of aminoacetonitrile afforded 1-*ethoxyhexylideneaminoacetonitrile* (I) which with potassium ethoxide and ethyl formate in ether was converted into the *potassium*

derivative of α-(1-ethoxyhexylideneamino)-β-hydroxyacrylonitrile (II). Schotten–Baumann benzoylation of (II) yielded the O-*benzoyl* derivative. The action of 2 : 4-dinitrophenylhydrazine in hydrochloric acid on (II) and on its carbethoxy-analogue (III) was examined in passing. The latter afforded the yellow 2 : 4-dinitrophenylhydrazone (IV) of ethyl *n*-amylpenaldate : the product from (II), though having the analogous composition of an amylpenaldonitrile 2 : 4-dinitrophenylhydrazone, was dark red and is regarded as *5-amino-2-n-amyloxazole-4-aldehyde 2 : 4-dinitrophenylhydrazone* [V; R = $NH{\cdot}C_6H_3(NO_2)_2$], or a tautomeric 5-imino-oxazoline form [VI; R = $NH{\cdot}C_6H_3(NO_2)_2$]. Ethyl benzamidocyanoacetate (VII) has been shown to isomerise readily to ethyl 5-amino-2-phenyloxazole-4-carboxylate (VIII) (I.C.I. Ltd., "The Chemistry of Penicillin", Chap. XXI) and it seems probable that [V; R = $NH{\cdot}C_6H_3(NO_2)_2$] was similarly formed from the open-chain penaldonitrile derivative.

The action of benzylamine on (II) produced a substance which is formulated as *5-amino-4-benzyliminomethyl-2-n-amyloxazole* (V; R = CH_2Ph) or the tautomeric *5-imino-2-n-amyl-4-benzylaminomethylene-4 : 5-dihydro-oxazole* (VI; R = CH_2Ph); the close resemblance of the ultra-violet absorption spectrum to that of an analogous oxazolone renders the latter formula preferable. The same substance has been obtained from benzylamine and the formylation product of hexamidoacetonitrile (Cornforth and Fawaz, "The Chemistry of Penicillin," Chap. XXI).



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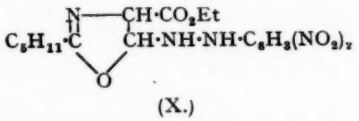
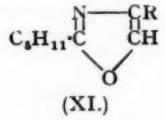


(X.)



(XI.)

The hydrolysis of imido-ethers by acids normally does not produce amides, but causes fission to an amine and an ester. It seems unlikely, therefore, that hydrolysis at the imido-ether linkage is responsible for the formation of (IV) from (III) and of the analogous nitriles (later rearranged to amino-oxazoles) from (II). It appears more probable that the action, *e.g.*, of 2 : 4-dinitrophenylhydrazine on (III) proceeds through an adduct (IX) to the oxazoline (X) (displacement of ethoxyl in the imido-ether) which then undergoes scission or hydrolysis at C5 to produce (IV). It may be noted that, although (IV) is produced at room temperature from ethyl 2-*n*-amyloxazole-4-carboxylate (XI; R = CO_2Et) and 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid (Cornforth and Cornforth, "The Chemistry of Penicillin," Chap. XXI), yet the same ester is unaffected by the acid alone; and it would seem that the intermediate (X) is involved here too.

The action of hydrogen chloride in ether, or better of boiling acetic acid, on (II) gave the expected *4-cyano-2-n-amyloxazole* (XI; R = CN), the structure of which was confirmed by hydrolysis to the known 2-*n*-amyloxazole-4-carboxylic acid amide and subsequently to the free acid.

Experimental.

1-Ethoxyhexylideneaminoacetonitrile (I).—A mixture of *n*-amyl cyanide, dry ethanol, and dry hydrogen chloride in equimolar amount was kept at 0° for 7—10 days. The liquid was decomposed in the usual manner with potassium carbonate and ether, and distilled, b. p. 68—77°/11 mm. (55—60 g. from 60 g. of amyl cyanide); it consisted largely of heximidoethyl ether but contained some unreacted nitrile. This product (25 g.) in ether (25 c.c.) was shaken vigorously with a solution of aminoacetonitrile hydrochloride (16 g.; or an equivalent amount of the hydrogen sulphate) in water (16 c.c.) for 15 minutes; the ethereal layer was washed well with water and dried (Na_2SO_4). On distillation *1-ethoxyhexylideneamino-acetonitrile* (16 g.) was collected, b. p. 70—71°/0·15 mm. (Found: C, 66·2, 66·2; H, 10·1, 9·8. $C_{10}H_{18}ON_2$ requires C, 65·9; H, 9·9%).

Potassium Salt of α-(1-Ethoxyhexylideneamino)-β-hydroxyacrylonitrile (II).—Potassium ethoxide was made under anhydrous conditions from the metal (3·6 g.), ethanol (10 c.c.), and ether (35 c.c.); the solution after dilution with ether to 350 c.c. was cooled to −10° and treated with a cooled mixture of the above nitrile (16 g.) and ethyl formate (7 g.). After two hours at −15° the mixture was left at 0° overnight, and the pale yellow *potassium* salt (15 g.) collected, washed quickly with ether, and dried in a vacuum (Found: N, 10·8. $C_{11}H_{17}O_2N_2K$ requires N, 11·3%). With dilute alcoholic ferric chloride the characteristic reaction was observed (*J.*, 1947, 96).

α-(1-Ethoxyhexylideneamino)-β-benzoyloxyacrylonitrile.—Benzoyl chloride (1 c.c.) was added dropwise with stirring to an ice-cooled solution of the potassium salt (II; 1·5 g.) in sodium hydroxide (0·5 c.c. of 2N). After one day, ether extraction and distillation of the dried extract at 14 mm. pressure gave the O-*benzoyl* derivative as an oil (Found: C, 68·6; H, 7·3; N, 8·7. $C_{18}H_{22}O_2N_2$ requires C, 68·8; H, 7·0; N, 8·9%). In alcohol the substance gave no colour with ferric chloride; after gentle warming with N-sodium hydroxide, however, the characteristic test was again positive on neutralisation.

Reaction of Potassium Salts (II) *and* (III) *with 2 : 4-Dinitrophenylhydrazine.*—Addition of the potassium salt (II) to excess of the hydrazine in 2N-hydrochloric acid precipitated a colourless oil which changed to a red solid on shaking. Recrystallisation from ethanol gave the *2 : 4-dinitrophenylhydrazone*

[V or VI; R = NH·$C_6H_3(NO_2)_2$], dull red prisms, m. p. 175° (Found: C, 49·7; H, 5·0. $C_{15}H_{18}O_5N_6$ requires C, 49·6; H, 5·2%). In the same manner the potassium salt (III) afforded bright yellow silky needles of ethyl *n*-amylpenaldate 2 : 4-dinitrophenylhydrazone (IV), m. p. 166° (Found: C, 50·1; H, 5·5. Calc. for $C_{17}H_{23}O_7N_5$: C, 49·8; H, 5·6%).

5-Imino-2-n-amyl-4-benzylaminomethylene-4 : 5-dihydro-oxazole (VI; R = CH_2Ph).—Benzylamine (0·5 c.c.) was dropped into a rapidly stirred solution of the potassium salt (II) (1·2 g.) in water (5 c.c.). The mixture was brought slowly to pH 7 by dropwise addition of 2N-hydrochloric acid. The yellow gummy precipitate was collected, dried, and triturated with ether. Recrystallisation from benzene–light petroleum (b. p. 40—60°) gave the *imino-oxazoline* in minute, faintly yellow prisms, m. p. 126—127° (Found: C, 70·9; H, 7·8; N, 15·4. $C_{14}H_{21}ON_3$ requires C, 70·8; H, 7·8; N, 15·5%). The m. p. was unchanged by admixture with the product obtained by Cornforth and Fawaz (*loc. cit.*). The absorption spectrum showed maxima at 3090 A. (ε, 10,550) and 2310 A. (ε, 8400). 2-Benzyl-4-benzylaminomethylene-4 : 5-dihydro-oxazol-5-one shows maxima at 3200 A. and 2400 A. (Merck & Co., "Penicillin Monograph", M-12c, 30).

4-Cyano-2-n-amyloxazole (XI; R = CN).—The potassium salt (II) (1 g.) was added during two minutes to boiling acetic acid (5 c.c.). The cooled solution was diluted with water, made alkaline with sodium hydroxide, and extracted with ether. The dried ethereal extract was distilled; the *cyano*-compound (0·5 g.), a colourless oil, had b. p. 130°/12 mm. The analytical sample was twice redistilled (Found: C, 66·2, 65·9; H, 7·7, 7·3; N, 16·6. $C_9H_{12}ON_2$ requires C, 65·8; H, 7·3; N, 17·1%). The nitrile (0·4 g.) was warmed with sodium hydroxide (4 c.c. of 2N) on a steam-bath until dissolved (24 hours). On cooling, 2-*n*-amyloxazole-4-carboxylic acid amide (0·2 g.) separated, m. p. and mixed m. p. 151°. Further hydrolysis (2N-alkali; refluxing for 2 hours) gave 2-*n*-amyloxazole-4-carboxylic acid, m. p. and mixed m. p. 94° (Cornforth and Cornforth, *op. cit.*).

We thank the British Council for enabling one of us (H. T. H.) to take part in this work.

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401. *Acidity Functions. Part I. Dissociation of Hydrogen Chloride in, and Proton Affinities of, Some Oxygen-containing Solvents.*

By ERNEST A. BRAUDE.

The nature of solutions of "strong" acids in non-aqueous solvents can be investigated by means of the acidity function H, first introduced by Hammett (cf. *Chem. Reviews*, 1935, **16**, 67). *p*-Nitroaniline being used as proton acceptor, H has been determined spectrometrically for 0·2—1M-solutions of hydrogen chloride in water and three organic oxygen-containing solvents. The variation of H with the acid concentration (c_A) can be represented by $H = m + n \log c_A$, where n has values close to unity in water, ethanol, and acetone, and a value of 0·5 in dioxan. These results indicate that in the range of acid concentrations studied, the dissociation of hydrogen chloride is large or complete in the first three solvents, but only small in dioxan, in agreement with evidence derived from conductivity measurements as far as these are available.

The equilibrium constants (K_B^S) of the proton-transfer reactions $SH^+ + B \rightleftharpoons BH^+ + S$, where SH^+ represents the solvated proton and B the proton-accepting indicator, can be calculated from H and are found to increase in the sequence water <dioxan <ethanol <acetone. Since K_B^S is an inverse measure of the proton-affinity of the solvent S, this is the sequence to be expected from simple considerations of decreasing electron-availability at the oxygen atom in the series ether >alcohol > water > ketone, except that the position of water is anomalous. The exceptionally high proton-affinity of water is further discussed in the following paper.

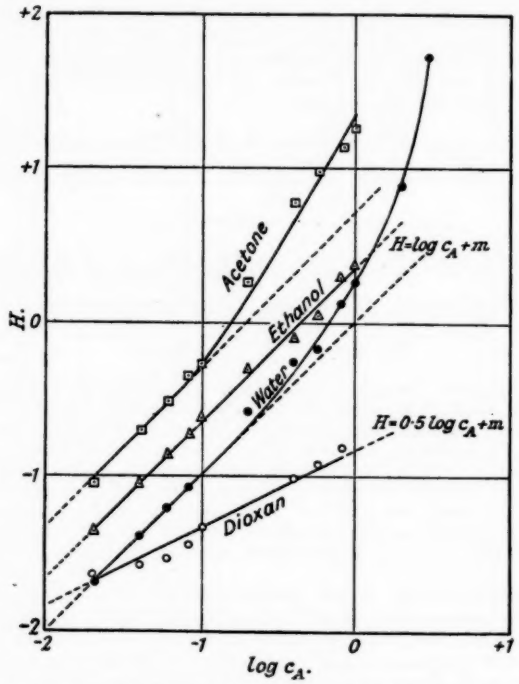
THE question of the nature of solutions of the so-called "strong" acids in solvents other than water has received much attention. Considerable information is now available regarding a number of individual solvent systems, but comparatively little progress has been made in establishing quantitative scales of comparison of such properties as proton-availability in different solvents. Apart from its intrinsic interest, this subject is of obvious importance to the interpretation of acid catalysis in non-aqueous solutions.

A quantity suitable for comparison of proton-availabilities is represented by the acidity function H, first introduced by Hammett (*loc. cit.*; Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721; Hammett and Paul, *ibid.*, 1934, **56**, 827; Hammett, "Physical Aspects of Organic Chemistry," McGraw Hill, New York, 1940; cf. Lewis and Biegeleisen, *J. Amer. Chem. Soc.*, 1943, **65**, 1144; Schwarzenbach and Sulzberger, *Helv. Chim. Acta*, 1944, **27**, 348) to deal with concentrated aqueous solutions of strong acids. The acidity function is an extension of the familiar indicator method of determining hydrogen-ion concentration in dilute aqueous solution, which depends on the colorimetric or spectrometric determination of the indicator ratio I, defined by $I = [BH^+]/[B]$, where B represents the indicator and BH^+ its conjugate acid. In dilute solution, the reaction $B + H^+ \rightleftharpoons BH^+$ obeys the mass law $K_B = [BH^+]/[B][H^+]$

where K_B is the indicator constant,* and $[H^+]$ is then directly proportional to I. In more concentrated acid solution, the classical mass law no longer applies, but I still represents a quantitative measure of the tendency of the solution to donate a proton to a neutral base. In order to provide a common basis for the use of different indicators, dilute aqueous solution is chosen as a reference state and H is defined by

$$H = \log ([BH^+]/[B]) - \log K_B^{H_2O} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $K_B^{H_2O}$ is the indicator constant in dilute aqueous solution. (The acidity function H as defined here is the negative value of Hammett's acidity function H_0. The present definition is preferred because H, unlike H_0, *increases* with *increasing* proton-availability.) The only assumption involved is that the ratio of different indicator constants is independent of the medium, and this is likely to be true for indicators of similar type. If only one indicator is employed, this question does not arise, and H, like I, is a direct experimental quantity.



The dependence of acidity function on hydrogen chloride concentration in water, dioxan, ethanol, and acetone.

In the present work, the acidity functions of solutions of hydrogen chloride in water and three other oxygen-containing solvents have been determined over a wide range of acid concentration, *p*-nitroaniline being used as indicator. The indicator ratios I were determined spectrophotometrically. If Beer's law is obeyed, and if ε_N and ε_S are the extinction coefficients at a chosen wave-length of the indicator B and its conjugate acid BH^+ in neutral solution, then $I = (\varepsilon_N - \varepsilon_A)/(\varepsilon_A - \varepsilon_S)$, where ε_A is the extinction coefficient in a given acid solution. Since the ultra-violet and the visible light absorption of an aromatic amine $R{\cdot}NH_2$ become identical, or nearly so, with that of the parent compound RH in sufficiently strong acid solution, ε_S can be derived from the light absorption of nitrobenzene. The location of the absorption band associated with the $R{\cdot}NH_2$ system is usually somewhat displaced in acid solution, and in order to minimise these medium effects, ε_N is determined at the wave-length position (λ_N) of the maximum in neutral solution, while ε_A and ε_S are determined at the wave-length position (λ_A) of the maximum in the acid solution. The spectrometric method of determining I is thus much to be preferred to the colorimetric one (cf. Flexser, Hammett, and Dingwall, *J. Amer. Chem.*

* The indicator constant K_B as defined here is the reciprocal of the indicator constant K_a employed by Hammett (*loc. cit.*).

Soc., 1935, **57**, 2103), not merely because it allows of a higher accuracy in the estimation of absorption intensities, but also because spectral resolution makes it possible largely to eliminate the effects of a change in medium on the light absorption. This is of especial importance in non-aqueous media where these effects tend to be larger than in aqueous solution. A further advantage of the spectrometric method is that the choice of indicator is not limited to those showing selective light absorption in the visible range of the spectrum. The band maximum of *p*-nitroaniline does, in fact, lie in the near ultra-violet region, though it has been employed by Hammett and Paul (*loc. cit.*) in their colorimetric determinations of H_0.

The choice of indicators is governed by two main considerations: the light-absorption properties, which should be such that ε_N is as large and ε_S as small as possible, and the base strength, which must be such that the ratio $[BH^+]/[B]$ has a suitable value in the acid solutions concerned. It can readily be shown (see Experimental) that the error in I consequent upon a given error in ε_A is least if ε_A has a value close to $\sqrt{\varepsilon_N\varepsilon_S}$, when the accuracy in I is about equal to that in ε_A, *i.e.*, *ca.* 2% in the present spectrometric work. For *p*-nitroaniline, the outer limits of I for an error in I not exceeding 10% are *ca.* 0·2 and 20. The range of solutions studied could be covered within these limits of I by using a single indicator.

The results of the measurements are collected in Table I. For water, the plot of I against c_A is linear up to $c_A = 0{\cdot}1$M, and $K_B^{H_2O}$, the limiting slope, has the value 9·0. The acidity functions are therefore given by $H = \log I - 0{\cdot}954$, and the values thus obtained are set out in Table II. For acid concentrations up to about 0·1M in water and acetone, and up to about 1M in ethanol and dioxan, the plots of H against c_A are linear (see Fig.), *i.e.*, H can be expressed in the form $H = n \log c_A + m$. The values of the slopes n are 1·00, 1·05, and 1·05 in water, ethanol, and acetone, respectively, and 0·50 in dioxan. At higher acid concentrations n increases with c_A. The relative magnitudes of H in the different solvents at one acid concentration are somewhat dependent on the latter, but mostly increase in the order dioxan < water < ethanol < acetone.

TABLE I.

Indicator ratios for *p*-nitroaniline in solutions of hydrogen chloride: c_A = acid concentration (mol./l.); λ_N, ε_N refer to the wave-lengths (mμ) and molecular extinction coefficients of the maxima in neutral solution; λ_A, ε_A refer to the acid solutions; ε_S is the extinction coefficient of nitrobenzene at λ_A in the same solvent; $I = (\varepsilon_N - \varepsilon_A)/(\varepsilon_A - \varepsilon_S)$.

	Water. $\lambda_N = 378$, $\varepsilon_N = 12{,}800$.				Dioxan. $\lambda_N = 353$, $\varepsilon_N = 15{,}400$.			
c_A.	λ_A.*	ε_A.	ε_S.	I.	λ_A.	ε_A.	ε_S.	I.
0·02	378	10,800	50	0·18	353	12,900	150	0·20
0·04	378	9,400	50	0·36	353	12,500	150	0·23
0·06	378	8,300	60	0·55	353	12,200	150	0·26
0·08	376	7,400	60	0·73	353	11,700	150	0·32
0·10	373	6,800	80	0·89	353	11,000	150	0·40
0·20	373	3,800	80	2·42	353	9,500	150	0·63
0·40	373	2,200	80	4·91	353	8,400	150	0·84
0·60	373	1,400	80	8·63	353	6,900	150	1·26
0·80	371	980	90	13·2	351	6,500	160	1·40
1·00	371	715	90	19·3	340	3,500	180	3·60
2·00	*360*	320	150	69	—	—	—	—
3·00	*360*	175	150	500	—	—	—	—
4·00	*360*	150	150	—	—	—	—	—

	Ethanol. $\lambda_N = 374$, $\varepsilon_N = 15{,}200$.				Acetone. $\lambda_N = 366$, $\varepsilon_N = 15{,}800$.			
c_A.	λ_A.	ε_A.	ε_S.	I.	λ_A.*	ε_A.	ε_S.	I.
0·02	373	11,000	60	0·39	366	8400	85	0·89
0·04	373	8,400	60	0·81	366	5500	85	1·89
0·06	373	6,900	60	1·21	366	4200	85	2·82
0·08	373	5,700	60	1·68	366	3100	85	4·23
0·10	373	4,800	60	2·19	365	2800	85	4·80
0·20	373	2,800	60	4·52	365	950	85	17·1
0·40	372	2,000	60	6·80	*362*	310	100	74
0·60	372	1,500	60	9·50	*351*	330	150	86
0·80	371	860	65	17·9	*350*	290	160	120
1·00	368	720	70	22·3	*350*	260	160	155

* Figures in italics signify that there is no clearly discernible maximum, but only an inflection or "bend" at this wave-length.

TABLE II.

Acidity functions for hydrogen chloride derived from indicator ratios of *p*-nitroaniline: $H = \log I - 0{\cdot}954$.

c_A.	Water.	Dioxan.	Ethanol.	Acetone.	c_A.	Water.	Dioxan.	Ethanol.	Acetone.
0·02	−1·70	−1·65	−1·36	−1·05	0·40	−0·26	−1·03	−0·12	+0·92
0·04	−1·40	−1·59	−1·04	−0·68	0·60	−0·18	−0·94	−0·02	+0·98
0·06	−1·21	−1·54	−0·87	−0·50	0·80	+0·17	−0·81	+0·30	+1·13
0·08	−1·09	−1·45	−0·73	−0·33	1·00	+0·33	−0·40	+0·39	+1·24
0·10	−1·01	−1·35	−0·62	−0·27	2·00	+0·89	—	—	—
0·20	−0·57	−1·15	−0·30	+0·28	3·00	+1·75	—	—	—

The indicator ratio is governed by the three equilibria

$$\text{(i)}\quad HA + S \overset{K_1}{\rightleftharpoons} SH^+ + A^-$$

$$\text{(ii)}\quad SH^+ + B \overset{K_2}{\rightleftharpoons} BH^+ + S$$

$$\text{(iii)}\quad HA + B \overset{K_3}{\rightleftharpoons} BH^+ + A^-$$

where HA represents the undissociated acid and SH^+ the solvated proton. When the indicator concentration is small compared with the acid concentration, equilibrium (iii) may be neglected in comparison with (i) and (ii), hence

$$I = [BH^+]/[B] = K_2[SH^+]f_{SH^+}f_B/[S]f_{BH^+}f_S \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where f's represent activity coefficients; the factors containing these are completely symmetrical and may be assumed to be unity, hence

$$I = K_2[SH^+]/[S] = K_B^S[SH^+] = K_B^S\alpha c_A \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and

$$H = \log (K_B^S/K_B^{H_2O}) + \log \alpha c_A$$

where K_B^S is the indicator constant * for the solvent S, and α the degree of dissociation of the acid. If α is large, $[SH^+] \sim c_A$ and $H = (K_B^S/K_B^{H_2O}) + \log c_A$. If α is small, $[SH^+] \sim \sqrt{K_A c_A}$ and $H = \log (K_B^S/K_B^{H_2O}) + 0{\cdot}5 \log K_A c_A$, where K_A is the dissociation constant of the acid. The fact that the slopes of the H–c_A plots have values close to unity in water, ethanol, and acetone, and a value of 0·5 in dioxan, therefore indicates that the dissociation of hydrogen chloride is large or complete in the first three solvents, but only small in dioxan at concentrations above 0·02M.

These findings are in agreement with evidence derived from conductivity measurements. The complete or nearly complete dissociation of hydrogen chloride in water is generally accepted. Data for ethanol (Goldschmidt, *Z. physikal. Chem.*, 1915, **89**, 129; 1916, **91**, 46; 1927, **108**, 121; Murray-Rust and Hartley, *Proc. Roy. Soc.*, 1929, *A*, **126**, 84; Bezman and Verhoek, *J. Amer. Chem. Soc.*, 1945, **67**, 1330) lead to a value of 0·011 for the thermodynamic dissociation constant of hydrogen chloride in this solvent. Taking the mean activity coefficient as 0·24 for $c_A = 0{\cdot}1$M (Butler and Robertson, *Proc. Roy. Soc.*, 1929, *A*, **125**, 694), a value of 0·7 is obtained for α. The only data available for acetone appear to be those of Kahlenberg and Lincoln (*J. Physical Chem.*, 1899, **3**, 12) and Sackur (*Ber.*, 1902, **35**, 1248). (Details of more recent measurements cited by Murray-Rust, Hartley *et al.*, *Ann. Reports*, 1930, **27**, 326, have not been published.) On plotting Sackur's values of Λ against $\sqrt{c_A}$, and extrapolating to $c_A = 0$, a value of 12·7 is obtained for Λ_0, the equivalent conductivity at infinite dilution. The value of the initial slope of the Λ–$\sqrt{c_A}$ curve is 90, which is very much *lower* than the theoretical one of 350 calculated by Onsager's equation (cf. Davies, "The Conductivity of Solutions," Chapman and Hall, London, 1930), and thus does not readily permit of the calculation of the true degree of dissociation. An approximate measure of α should be given by $\Lambda/\Lambda_0 - k\sqrt{\alpha c_A}$, where k is the observed slope; this leads to $\alpha > 1$, indicating large or complete dissociation. No measurements at all appear to have been made in dioxan, but solutions of hydrogen chloride in the related solvent ethyl ether have been examined by Kablukoff (*Z. physikal. Chem.*, 1899, **4**, 429) and by Mounajed (*Compt. rend.*, 1933, **197**, 44). Extrapolation of Mounajed's results gives values of 0·016 for Λ_0 and of 0·07 for the limiting slope of the Λ–$\sqrt{c_A}$ curve. The latter is again lower than that required by Onsager's equation. Calculation of α as above gives the value 0·2 when $c_A = 0{\cdot}1$M, thus indicating only about 20% dissociation at this acid concentration. The

* In this and the following two papers K_Y^X represents the equilibrium constant of the reaction $XH^+ + Y \rightleftharpoons YH^+ + X$ in the solvent X, *i.e.*, $K_Y^X = [YH^+]/[XH^+][Y]$.

value for dioxan is likely to be of the same order (cf. Gordy and Martin, *J. Chem. Physics*, **1939**, **7**, 99).

The differences in the acidity functions for the four solvents may now be considered. These will be due to differences in both the equilibria (i) and (ii). Since $I = K_B^s \alpha c_A$, K_B^s can be calculated from I by using the values of α deduced from conductivity measurements. For $c_A = 0{\cdot}1$M, the values of I for water, dioxan, ethanol, and acetone are 0·9, 0·4, 2·2, and 4·8 (Table I), and α being taken as 1·0, 0·2, 0·7, and 0·9, the values of K_B^s are 9, 20, 31, and 53. (The accuracy of the values for acetone and dioxan are dependent on the uncertainty in α, but this is unlikely to affect the *sequence* of magnitudes.) Since K_B^s is an inverse measure of the proton-affinity or basicity of the solvent relative to the indicator, these values indicate basicities decreasing in the order water > dioxan > ethanol > acetone. The order of basicity expected from simple considerations of electron-availability at the oxygen atom for the formation of proton-solvates of the oxonium type, *e.g.*, R_2OH^+, ROH_2^+, H_3O^+, $R_2C{:}OH^+$ is ether > alcohol > water > ketone, since alkyl groups are electron-repelling relative to hydrogen, and since a double-bonded oxygen atom in a carbonyl compound is very electron-deficient compared with that in water. The sequence of basicities determined by the indicator constants is thus the expected one, except that the position of water is anomalous. The conclusion that water is a stronger base than ethanol is in agreement with evidence derived from the thermodynamic activity of hydrogen chloride in these two solvents (Heston and Hall, *J. Amer. Chem. Soc.*, **1934**, **56**, 1462) and from the effects of small concentrations of water on the catalytic properties (Goldschmidt, *Z. physikal. Chem.*, **1907**, **60**, 728; *Z. Elektrochem.*, **1914**, **20**, 473; Braude, *J.*, **1944**, 443), electrical conductivity (Goldschmidt, *Z. physikal. Chem.*, **1914**, **89**, 129; Bezman and Verhoek, *J. Amer. Chem. Soc.*, **1945**, **67**, 1330), and indicator ratios (Lapworth and Partington, *J.*, **1910**, **97**, 19; Braude and Stern, following paper) of ethanolic solutions. The fact, indicated by the present results, that water also appears to be a stronger base than the ether dioxan is even more remarkable. The exceptionally high proton-affinity of water is further discussed in the following paper.

Experimental.

Materials.—Dioxan was purified by treatment with sodium (Hess and Frahm, *Ber.*, **1938**, **71**, 2629), b. p. 101°/760 mm., m. p. 12°. Ethanol (" Burnett absolute alcohol ") was dehydrated with magnesium ethoxide (Lund and Bjerrum, *Ber.*, **1931**, **64**, 210) until ε_A was constant. Acetone (" AnalaR ") was treated with potassium permanganate and distilled from potassium carbonate (Scheibe, May, and Fischer, *Ber.*, **1924**, **57**, 1330). *p*-Nitroaniline was crystallised from ethanol, m. p. 149°. Nitrobenzene was distilled in nitrogen, b. p. 93°/18 mm., n_D^{25} 1·5518. Acid solutions were prepared by passing hydrogen chloride, obtained by dropping concentrated hydrochloric acid (" AnalaR ") on concentrated sulphuric acid and dried over phosphoric oxide, into the solvent, and then diluting as required. Hydrogen chloride concentrations were determined by titration with sodium borate. All non-aqueous solutions were made up immediately before use and carefully protected from moisture.

Determination of the Indicator Ratio I.—For the technique of spectrometric measurements, see Braude, *J.*, **1945**, 490. The indicator concentration varied from 0·002 to 0·02%. ε's were independent of the indicator concentration within the experimental error (≯ ± 2%). The data for the neutral solutions agree closely with those of Morton and McGookin (*J.*, **1934**, 901) for ethanol, and of Dede and Rosenberg (*Ber.*, **1934**, **67**, 147) for water and dioxan. The error in I relative to the error in ε_A is given by

$$Z = (dI/I)/(d\varepsilon_A/\varepsilon_A) = \varepsilon_A(\varepsilon_S - \varepsilon_N)/(\varepsilon_N - \varepsilon_A)(\varepsilon_A - \varepsilon_S) \quad \ldots \quad (4)$$

Z has a minimum value when $\varepsilon_A = \sqrt{\varepsilon_S \varepsilon_N}$. If ε_S is small compared with ε_N, as in the case of *p*-nitroaniline, $Z_{min.} \sim 1$, *i.e.*, the errors in ε_A and I are nearly equal when ε_A has a value of the order of $\sqrt{\varepsilon_S \varepsilon_N}$, and (4) reduces to $Z \sim (I + 1)/I$, from which the lower limit of I for a given limit of error in I can readily be calculated. Thus, if the error in ε_A is 2% and the error in I is not to exceed 10%, then $Z = 5$ and the lower limit of I is 0·25. The upper limit of I for a given limit of error in I can be calculated by (4) using the constants for the indicator, but owing to the intrinsic uncertainty in ε_S and owing to the fact that the absorption band becomes ill-defined as ε_A approaches ε_S, this limit is somewhat lower than indicated by equation (4). In the present case, it is estimated that the error in I does not exceed 10% for the values of I up to about 20. As would be expected, the present values of I for the aqueous solutions differ somewhat from those previously obtained colorimetrically by Hammett and Paul (*loc. cit.*).

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402. *Acidity Functions. Part II. The Nature of Hydrogen Ion in Some Aqueous and Non-aqueous Solvents. The Exceptional Solvating Properties of Water.*

By Ernest A. Braude and E. S. Stern.

Acidity functions H have been determined for solutions of hydrogen chloride in binary mixtures of water, dioxan, ethanol, and acetone, using *m*- and *p*-nitroanilire as indicators. In water–dioxan, water–ethanol, and water–acetone mixtures, H varies non-linearly with solvent composition, passing through a minimum in the region of equimolar proportions of the two components. This is in sharp contrast to the behaviour in ethanol–acetone and ethanol–dioxan mixtures, where the change of H with solvent composition is gradual. The non-linear variations of H in the partly aqueous media are paralleled by the corresponding changes in electrical conductivity, in the catalytic properties, and in the heats of transfer of hydrogen chloride as determined by E.M.F. measurements, and cannot be accounted for merely as dielectric-constant effects. They may be explained, however, in terms of the exceptionally high proton-affinity (cf. Part I, preceding paper) and the exceptional quasi-crystalline structure of water. On the addition of organic solvent to the aqueous medium, the tetrahedral lattice is gradually broken down, and owing to the denser packing and the smaller extent of intermolecular hydrogen-bonding between water molecules, the stability of the hydroxonium ions increases and the proton-donating properties of the medium fall. When the proportion of organic solvent becomes sufficiently large, the hydroxonium ions are finally replaced by organic solvates and H rapidly increases with decreasing water content. The value obtained for the equilibrium constant of the reaction $H_3O^+ + EtOH \rightleftharpoons EtOH_2^+ + H_2O$ is in agreement with that obtained from conductivity measurements.

In Part I (preceding paper), measurements were reported of the acidity function H for solutions of hydrogen chloride in water, dioxan, ethanol, and acetone. In the present work, the variation of H with solvent composition in binary mixtures of these four solvents has been determined. These data were required in connection with kinetic investigations of certain acid-catalysed

Table I.

Indicator ratios for *p*-nitroaniline–hydrochloric acid in water–dioxan, water–ethanol, and water–acetone mixtures: λ_N, ε_N refer to wave-lengths (mμ) and molecular extinction coefficients of the maxima in neutral solution; λ_A, ε_A refer to the acid solutions; ε_S is the extinction coefficient of nitrobenzene at λ_A in the same solvent. $I = (\varepsilon_N - \varepsilon_A)/(\varepsilon_A - \varepsilon_S)$.

Vol. % of organic solvent.*	Neutral.		0·1M-HCl.				1M-HCl.			
	λ_N.	ε_N.	λ_A.	ε_A.	ε_S.	I.	λ_A.	ε_A.	ε_S.	I.
				Dioxan.						
0	378	12,800	373	6,800	80	0·89	371	715	90	19·3
20	385	14,600	383	9,900	35	0·48	386	2,100	30	6·03
40	383	15,300	382	13,700	35	(0·12)	395	7,100	15	1·15
60	376	16,000	378	15,000	50	(0·07)	386	10,500	30	0·52
70	375	16,200	375	15,200	55	(0·07)	378	8,600	50	0·89
80	370	16,200	369	15,200	70	(0·07)	†	†	†	†
90	366	15,700	366	14,300	85	(0·10)	†	†	†	†
100	353	15,400	353	11,000	150	0·40	340	3,500	180	3·60
				Ethanol.						
0	378	12,800	373	6,800	80	0·89	371	715	90	19·3
20	385	13,800	387	8,700	25	0·59	379	1,500	50	8·50
40	385	15,300	388	12,800	20	(0·20)	385	4,200	30	2·64
60	384	16,200	386	14,000	25	(0·16)	382	7,200	35	1·26
70	380	16,400	382	14,300	35	(0·15)	380	8,200	40	1·04
80	378	16,400	379	15,600	40	(0·05)	380	8,200	40	1·04
90	378	16,200	378	15,300	40	(0·06)	380	6,200	40	1·62
100	374	15,200	373	4,800	60	2·19	368	720	70	22·3
				Acetone.						
0	378	12,800	373	6,800	80	0·89	371	715	90	19·3
20	385	13,800	384	9,700	35	0·42	387	2,000	25	5·98
40	384	15,200	384	14,000	35	(0·09)	386	4,900	25	2·11
60	379	16,200	379	15,300	45	(0·06)	380	7,800	40	1·08
70	377	16,200	379	15,800	45	(0·03)	377	8,100	45	1·01
80	376	16,200	374	16,000	55	(0·01)	375	5,800	50	1·81
90	374	16,000	372	15,300	65	(0·05)	374	950	50	16·7
100	366	15,800	365	2,800	85	4·80	*350*	260	160	155

* For the precise meaning of " vol. % ", see Braude and Stern, this vol., p. 1984.
† The components form a two-phase system in this range.

TABLE II.

Indicator ratios for *m*-nitroaniline–0·1M-hydrochloric acid in water–organic solvent mixtures. For meaning of symbols, see Table I.

Vol. % of organic solvent.	λ_N.	ε_N.	λ_A.	ε_A.	ε_B.	I.
			Dioxan.			
40	368	1450	352	350	155	5·7
60	372	1450	370	600	70	1·6
70	373	1550	375	700	55	1·3
80	373	1600	377	780	50	1·1
90	373	1600	370	550	70	2·2
			Ethanol.			
40	364	1450	*348*	310	170	8·1
60	367	1450	362	480	90	2·5
70	369	1450	365	550	85	1·8
80	372	1450	366	640	85	1·5
90	373	1450	366	620	85	1·6
			Acetone.			
20	360	1550	*345*	275	190	15
40	371	1600	*355*	350	130	5·7
60	378	1600	370	610	70	1·8
70	380	1600	375	760	50	1·2
80	380	1650	376	860	45	1·0
90	380	1600	372	810	90	1·1

TABLE II*a*.

Indicator ratios and indicator constant of *m*-nitroaniline in water; c_A = hydrochloric acid concentration; $K_B^{H_2O} = I/c_A$.

c_A.	λ_N.	ε_N.	λ_A.	ε_A.	ε_B.	I.	$K_B^{H_2O}$.
0·001	356	1450	355	1020	160	0·27	270
0·005	356	1450	355	750	160	1·35	270
0·01	356	1450	355	510	160	2·7	270

TABLE III.

Indicator ratios for *p*-nitroaniline–0·1M-hydrochloric acid in anhydrous ethanol–dioxan and ethanol–acetone mixtures. For meaning of symbols, see Table I (ε_B has been neglected in calculating I).

	Ethanol–dioxan.						Ethanol–acetone.				
Vol. % of dioxan.	λ_N.	ε_N.	λ_A.	ε_A.	I.	Vol. % of acetone.	λ_N.	ε_N.	λ_A.	ε_A.	I.
0	373	15,200	373	4,800	2·17	0	373	15,200	373	4800	2·17
10	371	16,000	371	4 800	2·34	10	372	15,600	371	4900	2·18
20	371	16,000	371	4 800	2·34	20	372	15,200	371	5000	2·24
30	369	16,300	370	4,800	2·40	30	371	16,300	371	5000	2·26
40	367	16,500	369	5,200	2·17	40	371	16,400	369	5000	2·28
50	366	16,500	368	5,200	2·17	50	370	16,400	369	4800	2·41
60	365	17,100	364	5,400	2·16	60	369	16,400	369	4800	2·41
70	363	17,100	361	5,500	2·09	70	369	16,500	369	4100	3·03
80	362	16,600	359	5,900	1·81	80	369	16,500	369	3800	3·34
90	360	16,300	359	7,700	1·18	90	368	16,200	369	3600	3·50
100	353	15,400	353	11,000	0·40	100	366	15,800	365	2800	4·64

reactions (cf. Braude and Stern, following paper) and it was also hoped that they would throw more light on the abnormally high proton-affinity of water indicated by the earlier work.

As previously, acidity functions were determined spectrophotometrically, *p*-nitroaniline being used as indicator as far as possible. Measurements were made at two acid concentrations, 0·1 and 1M. At the lower concentration the indicator ratios obtained with *p*-nitroaniline for the water–organic solvent mixtures containing 40 to 90% (by vol.) of organic solvent were too small to be of sufficient accuracy (Table I) and for these solutions a more basic indicator was required. *m*-Nitroaniline, which fulfils the desirable condition (cf. Part I) of close structural relationship to *p*-nitroaniline and has a base strength of the required order, was employed, although its light-absorption properties are much less suitable than those of the *p*-isomer, the difference in intensities of the bands due to the base and its conjugate acid being only about one-tenth as great. The spectrometric data and indicator ratios for the various solvent mixtures are collected in Tables I—III. The value of the indicator constant $K_B^{H_2O}$ derived from solutions in dilute aqueous hydrochloric acid (Table II*a*) is 270 for *m*-nitroaniline as compared with 9 for *p*-nitroaniline.

The derived values of the acidity functions are given in Tables V and VI. In water–dioxan, water–ethanol, and water–acetone mixtures, H decreases strongly on the addition of the organic

TABLE IV.

Acidity functions of hydrogen chloride in aqueous solvent mixtures: m = mols. % of organic solvent; H = log $I_{p\text{-nitroaniline}}$ −0·954 or log $I_{m\text{-nitroaniline}}$ −2·43.

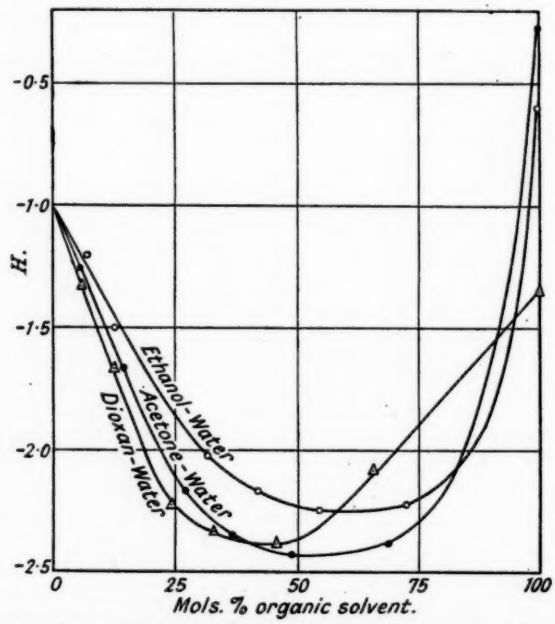
Vol. % of organic solvent.	Water–dioxan.			Water–ethanol.			Water–acetone.		
	m.	H (0·1M-HCl).	H (1M-HCl).	m.	H (0·1M-HCl).	H (1M-HCl).	m.	H (0·1M-HCl).	H (1M-HCl).
0	0	−1·01	+0·33	0	−1·01	+0·33	0	−1·01	+0·33
20	5·0	−1·27	−0·17	7·1	−1·18	−0·03	5·8	−1·33	−0·18
40	12·3	−1·67	−0·89	12·0	−1·52	−0·53	14·0	−1·67	−0·63
60	24·0	−2·23	−1·24	31·8	−2·03	−0·85	27·0	−2·17	−0·92
70	32·9	−2·32	−1·01	42·0	−2·17	−0·94	36·5	−2·35	−0·95
80	45·8	−2·39	—	55·2	−2·25	−0·94	49·5	−2·43	−0·70
90	65·2	−2·09	—	73·8	−2·23	−0·74	69·0	−2·39	+0·27
100	100	−1·35	−0·40	100	−0·61	+0·39	100	−0·27	+1·24

TABLE V.

Acidity functions of hydrogen chloride in non-aqueous solvent mixtures: m = mols. % of dioxan or acetone.

Ethanol–dioxan.				Ethanol–acetone.			
m.	H (0·1M-HCl).	m.	H (0·1M-HCl).	m.	H (0·1M-HCl).	m.	H (0·1M-HCl).
0	−0·61	50·6	−0·62	0	−0·61	54·4	−0·57
7·1	−0·58	61·4	−0·63	8·1	−0·61	64·8	−0·47
14·5	−0·58	73·2	−0·70	17·6	−0·60	76·1	−0·43
22·6	−0·57	86·0	−0·88	24·8	−0·60	88·0	−0·41
31·4	−0·62	100	−1·35	34·2	−0·59	100	−0·27
40·5	−0·62	—	—	44·3	−0·57	—	—

FIG. 1.



The dependence of acidity function on solvent composition in organic solvent–water mixtures. Concentration of hydrogen chloride 0·1M.

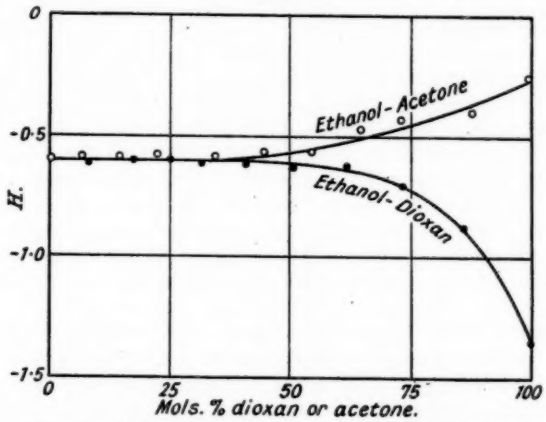
solvent to water, or of water to the organic solvent, and passes through a minimum in the region of equimolar proportion of the two components (Fig. 1). The curves are similar in shape at the two acid concentrations 0·1 and 1M, but the minima occur at somewhat lower proportions of organic solvent at the higher acid concentration. The behaviour of the aqueous solutions is in

sharp contrast to that of ethanol–acetone and ethanol–dioxan mixtures, where H exhibits no minima but varies gradually with solvent composition (Fig. 2).

The striking contrast in the variation of the acidity function with solvent composition in the partly aqueous as compared with the completely non-aqueous media shows that the peculiar features of the former must be associated with the component water. These features cannot be solely due to dielectric-constant or similar effects, since such effects should arise equally in ethanol–dioxan mixtures, the dielectric constants of which also cover a wide range (D = 30 to D = 2).

It has long been known that small concentrations of water have a very pronounced influence on the properties of hydrogen chloride in solvents such as methanol, ethanol, and acetone, both the electrical conductivity (Goldschmidt, *Z. physikal. Chem.*, 1914, **89**, 129; Hughes and Hartley, *Phil. Mag.*, 1933, **26**, 610; Bezman and Verhoek, *J. Amer. Chem. Soc.*, 1945, **67**, 1330) and the catalytic effects in certain acid-catalysed reactions (Goldschmidt, *Z. Elektrochem.*, 1914, **20**, 473 and earlier papers; Braude, *J.*, 1944, 443) decreasing rapidly with increasing water content. This phenomenon cannot be due to a decrease in the degree of dissociation of the acid, since the dissociation constant actually increases (Bezman and Verhoek, *loc. cit.*), and was first ascribed by Goldschmidt to the greater basicity of the water as compared with ethanol, and

FIG. 2.



The dependence of acidity function on solvent composition in ethanol–dioxan and ethanol–acetone mixtures. Concentration of hydrogen chloride 0·1M.

to the replacement of ethoxonium ions ($EtOH_2^+$) by hydroxonium ions (H_3O^+). Lapworth and Partington (*J.*, 1910, **97**, 19) showed that a similar decrease occurs in the indicator ratio of aminoazobenzene when small quantities of water are added to anhydrous solutions of hydrogen chloride in ethanol, and could be explained in the same way, and Kolthoff (*Pharm. Weekblad*, 1923, **60**, 22) employed the corresponding change in the indicator ratio of methyl-orange for the empirical determination of the water content of slightly aqueous ethanol. Some measurements with *p*-nitroaniline in this region of solvent composition are given in Table VI. From these data the equilibrium constant of the reaction

$$EtOH_2^+ + nH_2O \rightleftharpoons (nH_2O,H^+) + EtOH \quad . \quad . \quad . \quad . \quad . \quad (1)$$

can be calculated, if it is assumed that the minimum value of I (I') which is reached at a water concentration of about 20 vol. % (Table I) represents the point where the conversion of ethoxonium ions into water-solvated protons is complete. The ratio $[(nH_2O,H^+)]/[EtOH_2^+]$ is then given by $x = (I_0 - I)/(I - I')$, where I_0 is the indicator ratio in anhydrous ethanol and I that at a water concentration c_{H_2O}; and the equilibrium constant of reaction (1) is given by

$$K_{H_2O}^{EtOH} = \frac{[(nH_2O,H^+)]}{[EtOH_2^+][H_2O]^n} = \frac{x(x+1)^n}{(c_{H_2O} + xc_{H_2O} - nx\alpha c_A)^n} \quad . \quad . \quad . \quad . \quad (2)$$

where c_A is the acid concentration, and α the degree of dissociation of the acid.

In order to have a physical meaning, $K_{H_2O}^{EtOH}$ must be positive, *i.e.*, $nx\alpha c_A < (c_{H_2O} + xc_{H_2O})$. This condition can only be fulfilled with the present values of x (Table VI) if n, the number of

water molecules associated with each hydrogen ion, is less than 2. This must mean that, in fact, $n = 1$ and that in this range the hydroxonium ion is correctly represented by H_3O^+ as was first assumed, but not proved, by Goldschmidt (*loc. cit.*). The values of $K_{H_3O}^{EtOH}$ are satisfactorily constant for water concentrations from 0·05 to 0·5M (Table VI). The mean value of 13 is in reasonably good agreement with the mean value of 17 deduced by Goldschmidt and by Bezman and Verhoek (*loc. cit.*) from conductivity measurements, and in less good agreement with the value of 5 (Goldschmidt, *loc. cit.*) derived from kinetic data. The corresponding constant K_B^{EtOH} for the equilbrium between *p*-nitroaniline and ethoxonium ions in ethanol is 31 (Part I, *loc. cit.*) and water is thus a base almost half as strong as *p*-nitroaniline.

TABLE VI.

Indicator ratios for *p*-nitroaniline–0·1M-hydrogen chloride in slightly aqueous ethanol, and equilibrium constants $K_{H_3O}^{EtOH}$ (see text) of the reaction $EtOH_2^+ + H_2O \rightleftharpoons H_3O^+ + EtOH$: $\varepsilon_N = 15{,}200$, $\varepsilon_S] = 60$, $x = [H_3O^+]/[EtOH_2^+]$.

Vol. % of ethanol.	H_2O, mols./l.	ε_A.	I.	x.	$K_{H_3O}^{EtOH}$.	Vol. % of ethanol.	H_2O, mols./l.	ε_A.	I.	x.	$K_{H_3O}^{EtOH}$.
100	0·000	4800	2·19	—	—	99·4	0·336	9,800	0·55	3·28	13
99·9	0·056	5900	1·57	0·41	16	99·3	0·392	10,400	0·46	4·22	13
99·8	0·112	6900	1·22	0·83	13	99·2	0·448	10,800	0·41	4·95	14
99·7	0·168	7600	1·01	1·25	11	99·1	0·504	11,200	0·36	5·90	14
99·6	0·224	8300	0·83	1·75	11	99·0	0·560	11,600	0·31	7·25	15
99·5	0·280	9100	0·67	2·45	12					Mean	13

The decrease in H observed on passing from water to mixtures containing up to about 50 mols. % of organic solvent is again paralleled by a corresponding fall in electrical conductivity (Schukov and Dneprov, *J. Gen. Chem. Russia*, 1938, **8**, 1476; Owen and Waters, *J. Amer. Chem. Soc.*, 1938, **60**, 2371; Hartmann, *Z. physikal. Chem.*, 1941, *A*, **191**, 197), and again cannot be accounted for simply by a decrease in the degree of dissociation of the acid. In the case of water–ethanol mixtures, the dissociation constant (K_A) of hydrochloric acid remains very large up to a 90% molar proportion of ethanol (Bezman and Verhoek, *J. Amer. Chem. Soc.*, 1945, **67**, 1330). In water–dioxan mixtures, where the lowering of the dielectric constant is considerably greater, K_A does decrease with increasing concentration of dioxan, but much less rapidly than the corresponding fall in H. Thus, Owen and Waters (*loc. cit.*) give the values of K_A as *ca.* 1 and 0·01 for 45 and 70 weight % dioxan, respectively, corresponding to changes in the degree of dissociation of $\Delta \log \alpha = ca. -0{\cdot}15$ and -1 as compared with water ($\alpha = 1$). The corresponding changes in H are *ca.* $-1{\cdot}2$ and $-1{\cdot}9$. Since $H = \log (\alpha c_A K_B^s / K_B^{H_2O})$ (Part I, *loc. cit.*), and since the acid concentration c_A is a constant, the changes in H must therefore again be partly due to changes in $K_B^s/K_B^{H_2O}$, *i.e.*, in the indicator constant for the solvent relative to that for water. $K_B^s/K_B^{H_2O}$ can be calculated from H, c_A, and the value of α derived from conductivity measurements. The values obtained for water–ethanol mixtures are given in Table VII, α being taken as unity throughout except in 100% ethanol where it is taken as 0·7 (cf. Part I, *loc. cit.*).

TABLE VII.

Indicator constant ratios $K_B^s/K_B^{H_2O}$ for 0·1M-hydrochloric acid–water–ethanol mixtures, and free energies of transfer of hydrogen chloride from infinitely dilute aqueous solution.

Vol. % of ethanol.	$K_B^s/K_B^{H_2O}$.	$-RT\Delta \log K_B^s/K_B^{H_2O}$.	$\Delta(-\Delta H)$.*
0	1	—	—
20	0·66	+ 230	− 150
40	0·30	+ 570	+ 550
60	0·093	+1400	+2300
70	0·068	+1600	+2400
80	0·056	+1700	+2300
90	0·059	+1700	+2000
100	3·1	− 690	−3000

* Butler and Robertson, *Proc. Roy. Soc.*, 1929, *A*, **125**, 694.

If the earlier conclusion is correct, namely, that in media containing more than 20 vol. % of water, the hydrogen ions are exclusively solvated by water, then the change in K_B^s in this range of solvent composition must be due either to a change in the state of solvation or to the inconstancy of the activity-coefficient term (equation 2, Part I, *loc. cit.*), or to both. Even if the activity-coefficient term were not constant, it could only account for a small part of the variation in K_B^s, since the mean activity coefficient of hydrogen chloride itself only changes by a factor of

less than 5 on passing from water to ethanol or dioxan (Butler and Robertson, *Proc. Roy. Soc.*, 1929, *A*, **125**, 694; Harned *et al.*, *J. Amer. Chem. Soc.*, 1938, **61**, 59) and since the total variation in the symmetrical term $(f_{SH^+}\ f_B)/(f_{SH^+}\ f_S)$ is likely to be much smaller. It is therefore highly probable that the decrease in K_B^s which accounts for the left-hand part of the H–c_s curves in water–organic solvent mixtures (Fig. 1) is due to a change in the state of solvation of the hydrogen ions, and to an increase in the proton-affinity of water. A qualitative explanation of this effect may be given in terms of the quasi-crystalline tetrahedral structure which conditions the unique properties of water (Bernal and Fowler, *J. Chem. Physics*, 1933, **1**, 515) and in which the proton affinity of the individual water molecules is partly satisfied by hydrogen-bonding with neighbouring molecules. The protons are accommodated in the interstices of the tetrahedral lattice and bonded equally to the surrounding oxygen atoms, a picture in agreement with a solvation number of 4 (Ulich, " Hand- und Jahrbuch der chemischen Physik ", 1933, **6**, 186) for hydrogen ion in water. On the addition of an organic solvent to the purely aqueous medium, the open tetrahedral structure will be gradually broken down through the interposition of organic solvent molecules, and hydrogen-bonding between neighbouring water molecules will be partly replaced by much weaker hydrogen-bonding with organic solvent molecules. The density of packing will increase and the proton will be preferentially surrounded by the smaller water molecules (cf. Rao, *J. Indian Chem. Soc.*, 1945, **22**, 260). As a result of the smaller extent of intermolecular hydrogen bonding and of the closer packing of the solvation shell surrounding the protons, the effective proton affinity of the water molecules will increase, and the equilibrium $(nH_2O,H^+) + B \rightleftharpoons BH^+ + nH_2O$ will be displaced towards the left. As the proportion of organic solvent is increased, the aqueous solvation shell will be gradually dispersed and the aqueous solvates (nH_2O,H^+) will be replaced by hydroxonium ions H_3O^+. This state of affairs will correspond to the minima in the H–c_s curves. In the rising (right-hand) parts of the curves (Fig. 1) the hydroxonium ions are in turn replaced by organic oxonium ions of the type $EtOH_2^+$.

It thus appears that the effective proton-affinity of liquid water, though already unusually large (cf. Part I) is still much smaller than that of water in another solvent, and that the nature of the H–c_s curves in water–organic solvent mixtures is conditioned by the exceptional structure of water on the one hand, and its exceptionally high proton-affinity on the other. The cause of this high proton-affinity is not clear; it may be connected with the threefold symmetry of the hydroxonium ion. In the organic solvents, infra-red absorption and X-ray diffraction studies indicate that hydrogen-bonded structure is either much less prevalent, as in the case of ethanol (cf. Gordy, *J. Amer. Chem. Soc.*, 1938, **60**, 605; Pierce and MacMillan, *ibid.*, p. 779; Davies, *Ann. Reports*, 1946, **43**, 5), or largely absent, as presumably in acetone and dioxan, and consequently the deviations from linearity of the H–c_s curves in anhydrous mixtures are much less pronounced.

A measure of the change in the proton-affinity of the solvent will be given by $RT\Delta\log(K_B^s/K_B^{H_3O})$, which is the change in the free energy of the proton-transfer reaction $SH^+ + B \rightleftharpoons BH^+ + S$. The values obtained for the water–ethanol system are given in Table VII. They are of the same order of magnitude and vary in the same manner with the medium composition as the corresponding changes in the heat content of transfer of hydrogen chloride from water to the ethanolic solvent derived by Butler and Robertson (*loc. cit.*) from E.M.F. measurements of the cell $H_2|HCl,H_2O$–EtOH,AgCl|Ag. These authors pointed out that $-\Delta H$ should vary linearly with solvent composition if it depended only on changes in electrostatic solvation energy with dielectric constant and that the deviations signify another kind of interaction. The correspondence between $RT\Delta\log K_B^s/K_B^{H_3O}$ and $\Delta(-\Delta H)$ is in agreement with the view that both are controlled primarily by the change in the proton-affinity of the water and by the energy of " chemical " solvation of the proton. The displacement of the maxima in $-\Delta H$ (minima in H) towards lower ethanol proportions with increasing acid concentrations probably arises from the fact that the electrolyte assists in disrupting the quasi-crystalline water structure (cf. Stewart, *J. Chem. Physics*, 1943, **11**, 72; Hasted, Ritson, and Collie, *ibid.*, 1948, **16**, 1). Another indication of this effect is provided by the miscibility gap which occurs in the 1M-hydrogen chloride–water–dioxan system (Table I).

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403. *The Kinetics of Anionotropic Rearrangement. Part VIII. Medium Composition, Acidity Function, and Reaction Rate.*

By Ernest A. Braude and E. S. Stern.

The rates of acid-catalysed rearrangement of phenylpropenyl- and ethynylpropenyl-carbinol in water–dioxan, water–ethanol, and water–acetone mixtures have been determined over the entire range of medium composition at hydrochloric acid concentrations of 0·1 and 1M. The proportionality between rate constants and acidity function, previously noted when the acid concentration is varied at constant solvent composition (Part I, *J.*, 1944, 436), also holds when the solvent composition is varied at constant acid concentration. This relationship confirms a reaction mechanism involving a fast reversible proton-transfer followed by a slow rearrangement of the oxonium ion formed. Variations in the rate constants with medium composition are mainly due to variations in the proton-transfer equilibrium $ROH + SH^+ \rightleftharpoons ROH_2^+ + S$, where SH^+ represents the solvated proton.

The influence of medium composition on the rate of acid-catalysed anionotropic rearrangement has been investigated in earlier papers (cf. Parts II and V, *J.*, 1944, 443; 1946, 496). It was found that in water–ethanol– and water–dioxan–hydrochloric acid media the rate constants for a constant acid concentration vary strongly with solvent composition, passing through a minimum in the region of 80% by volume of organic solvent. These measurements have now been extended to cover the whole range of water–dioxan, water–ethanol, and water–acetone mixtures for the rearrangements of phenylpropenylcarbinol (I) in 0·1M-, and ethynylpropenylcarbinol (II) in 1M-hydrochloric acid. The main object of the study was to test whether the

$$\text{(I)}\ Ph{\cdot}CH(OH){\cdot}CH{:}CHMe \longrightarrow Ph{\cdot}CH{:}CH{\cdot}CH(OH)Me$$
$$\text{(II)}\ CH{:}C{\cdot}CH(OH){\cdot}CH{:}CHMe \longrightarrow CH{:}C{\cdot}CH{:}CH{\cdot}CH(OH)Me$$

correlation between the rate of rearrangement and the acidity function of the medium, previously established for the variation of acid concentration at constant solvent composition (Part I, *J.*, 1944, 336), also holds when the solvent composition is varied at constant acid concentration. The relevant acidity functions have now been determined (preceding paper).

The data are collected in Tables I and II. In all three solvent mixtures, the rate constants (k) initially decrease with increasing proportions of organic solvent, pass through a minimum when the concentration (c_s) of organic solvent reaches about 80% by volume, and finally increase again. The variations in k run parallel to those in the acidity function H, and the quantity $\log k - H$ is approximately constant.

Table I.

Rearrangements of phenylpropenylcarbinol (I) in 0·1M-hydrochloric acid at 30·0°: k = first-order rate constants × 10^4 min.$^{-1}$ (see Experimental); H = acidity functions of the medium (see preceding paper).

Vol. % of organic solvent.	Dioxan.		Ethanol.		Acetone.	
	k.	$\log k - H$.	k.	$\log k - H$.	k.	$\log k - H$.
20	21,000	5·59	—	—	—	—
40	7,500	5·55	8,700	5·46	10,700	5·70
60	2,100	5·55	2,400	5·41	3,500	5·71
70	1,230	5·48	1,350	5·30	2,100	5·57
80	690	5·23	890	5·20	1,680	5·66
90	620	4·88	740	5·10	1,360	5·52
100	5,700	5·11	25,000	5·01	42,000	5·35

Table II.

Rearrangements of ethynylpropenylcarbinol (II) in 1M-hydrochloric acid at 30·0°: k = first-order rate constants, H = acidity functions.

Vol. % of organic solvent.	Dioxan.		Ethanol.		Acetone.	
	k.	$\log k - H$.	k.	$\log k - H$.	k.	$\log k - H$.
20	103	2·18	111	2·08	98	2·17
40	30·5	2·37	43	2·16	35·5	2·08
60	11·7	2·31	15·3	2·03	13·3	2·04
70	10·2	2·02	7·7	1·83	10·4	1·97
80	*	*	5·1	1·65	15·3	1·88
90	*	*	4·9	1·53	150	1·91
100	75	2·28	77	1·50	14,900	1·93

* Medium components form a two-phase system.

The relation between H and log k affords a criterion of the reaction mechanism (cf. Hammett and Paul, *J. Amer. Chem. Soc.*, 1934, **56**, 830; 1936, **58**, 2182; Hammett and Zucker, *ibid.*, 1939, **61**, 2791). The two most likely mechanisms of rearrangement are (cf. Part VII, this vol., p. 794):

$$\text{(I.)}\quad \text{R·OH} \xrightarrow[k_1\ \text{slow}]{\text{H}^+} \text{R}^+ + \text{OH}_2 \xrightarrow[\text{fast}]{} \text{R'·OH}_2^+ \overset{\text{H}^+}{\rightleftharpoons} \text{R'·OH}$$

$$\text{(II.)}\quad \text{R·OH} \underset{K_1\ \text{fast}}{\overset{\text{H}^+}{\rightleftharpoons}} \text{R·OH}_2^+ \xrightarrow[k_2\ \text{slow}]{} \text{R'·OH}_2^+ \overset{\text{H}^+}{\rightleftharpoons} \text{R'·OH}$$

In (I) a slow formation of the carbonium ion by the reaction between the carbinol and a solvated proton (represented simply by H^+) is followed by a fast rearrangement of the carbonium ion. In (II) a fast formation of the oxonium ion by the reversible proton transfer from the solvent to the carbinol is followed by a slow unimolecular rearrangement of the oxonium ion. The overall rate constants will be given, respectively, by

$$\text{(I)}\quad k = k_1[\text{H}^+]\frac{f_{\text{ROH}}f_{\text{H}^+}}{f_{\text{X}}} \quad \ldots\ldots\ldots \quad (1)$$

$$\text{(II)}\quad k = K_1k_2[\text{H}^+]\frac{f_{\text{ROH}}f_{\text{H}^+}}{f_{\text{Y}}} \quad \ldots\ldots\ldots \quad (2)$$

where k's represent rate constants, K's equilibrium constants, and f's activity coefficients, and where X and Y refer to the transition states of the slow steps. Since no changes in charge-type are involved, the activity coefficient terms are likely to be constant and not very different from unity, so that $k = k_1[\text{H}^+]$ in (1) and $k = K_1k_2[\text{H}^+]$ in (2). Since both k_1 and k_2 should be largely independent of the solvent, variations of k with solvent composition at constant acid concentration can only be accounted for either by changes in the degree of dissociation of the acid, or by variations in the equilibrium constant K_1. Recent conductivity measurements (Bezman and Verhoek, *J. Amer. Chem. Soc.*, 1945, **67**, 1330) show that the dissociation of hydrogen chloride in aqueous ethanol remains practically complete up to 90% ethanol concentration and then decreases. An earlier suggestion (Part II, *loc. cit.*) that the over twenty-fold decrease in k between 20% and 80% ethanol is due to a decrease in the dissociation of the acid is thus incorrect, and the fact that log k can be expressed as a linear function of the dielectric constant must have a different significance. In aqueous dioxan the degree of dissociation does initially decrease with increasing dioxan concentration (Owen and Waters, *J. Amer. Chem. Soc.*, 1938, **60**, 2371) but much less rapidly than the corresponding fall in the rate constants. The large variations of k with solvent composition are thus not readily accounted for in terms of the carbonium-ion mechanism (I). They are to be expected, however, for the oxonium-ion mechanism (II), since the rate equation now involves the equilibrium constant K_1 of the proton-transfer reaction $\text{R·OH} + \text{H}^+ \rightleftharpoons \text{R·OH}_2^+$ and since it has been shown (preceding paper) that the corresponding equilibrium constants for the conversion of other neutral bases into their conjugate acids also vary with solvent composition, in a similar manner to k. Since $H = \log([\text{H}^+]K_{\text{B}}^{\text{S}}/K_{\text{B}}^{\text{H}_2\text{O}})$, where H is the acidity function and K_{B}^{S} and $K_{\text{B}}^{\text{H}_2\text{O}}$ are the equilibrium constants of the reaction $\text{B} + \text{H}^+ \rightleftharpoons \text{BH}^+$ in a solvent S and in water respectively, it is readily deduced from (2) that

$$\log k = H + \log(k_2/K_{\text{ROH}}^{\text{H}_2\text{O}}) \quad \ldots\ldots\ldots \quad (3)$$

where $K_{\text{ROH}}^{\text{H}_2\text{O}}$ is the equilibrium constant of the reaction $\text{H}_3\text{O}^+ + \text{ROH} \rightleftharpoons \text{ROH}_2^+ + \text{H}_2\text{O}$ in water, *i.e.*, log $k - H$ = constant. The relatively small deviations from the relationship apparent in Tables I and II are not surprising, since the acidity function is strictly independent of the indicator base (B) only for compounds closely related in structure (Braude, this vol., p. 1972), whereas the nitroanilines used in the determinations of H, because of their suitable physical properties, are quite different in type from the carbinols involved in the anionotropic rearrangements. The conclusion that the latter proceed by the oxonium-ion mechanism (II) is in agreement with independent evidence (cf. Part VII, *loc. cit.*).

The variations in k with solvent composition at constant acid concentration are thus to be ascribed primarily to changes in the equilibrium $\text{R·OH} + \text{SH}^+ \rightleftharpoons \text{R·OH}_2^+ + \text{S}$ and in the ratios $[\text{R·OH}_2^+]/[\text{R·OH}]$ due to changes in the proton affinity of the solvent.

Experimental.

The technique of kinetic measurements was that previously described (Parts I and V, *loc. cit.*); x% by volume of organic solvent stands for a medium obtained *by mixing* x ml. of organic solvent and $(100 - x)$ ml.of water containing the appropriate amount of hydrochloric acid to give a 0·1M- or 1M-solution. In practice, aqueous solutions were prepared by mixing x ml. of organic solvent, $(90 - x)$ ml. of water, and 10 ml. of 1M- or 10M-hydrochloric acid, and making up to 100 ml. with a mixture of x ml. of organic solvent and $(100 - x)$ ml. of water. The molar concentration of organic solvent is then given by $1800xd/[18xd + (100 - x)M]$, where d and M are its density and molecular weight, respectively. Anhydrous solutions were prepared immediately before use (Braude, this vol., p. 1975). In view of the considerable ultra-violet light absorption of acetone, the choices of the carbinol concentration and of the dilution ratio for the spectrometric assay were rather more critical than with the other solvents. Four typical runs are given below.

Rearrangements of phenylpropenylcarbinol in 0·1M-*hydrochloric acid at* 30·0°. [Carbinol concentration, 0·2% w/v. Acetone concentration, (*a*) 80%, (*b*) 100%.]

(*a*) Time, mins.	0	1	2	3	4	∞	
$E^{1\%}_{1\,cm.}$ (2510 A.)	30	220	410	520	600	1260	
10^4k (min.$^{-1}$)	—	1650	1660	1690	1710	—	(Mean) 1680
(*b*) Time, mins.	0	0·25	0·40	0·55	∞		
$E^{1\%}_{1\,cm.}$ (2510 A.)	30	850	1020	1120	1260		
10^4k (min.$^{-1}$)	—	44,000	41,000	40,000	—	(Mean) 42,000	

Rearrangements of ethynylpropenylcarbinol in 1M-*hydrochloric acid at* 30·0°. [Carbinol concentration, 0·5%. Acetone concentration, (*a*) 80%, (*b*) 100%.]

(*a*) Time, mins.	0	650	820	1000	1160	∞	
$E^{1\%}_{1\,cm.}$ (2230 A.)	—	830	940	1000	1080	1300	
10^4k (min.$^{-1}$)	—	15·6	15·8	14·8	15·0	—	(Mean) 15·3
(*b*) Time, mins.	0	0·20	0·40	0·60	∞		
$E^{1\%}_{1\,cm.}$ (2230 A.)	—	340	590	760	1300		
10^4k (min.$^{-1}$)	—	15,300	15,000	14,500	—	(Mean) 14,900	

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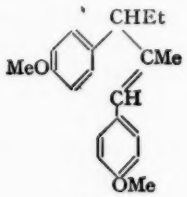
404. *Dimerides of Anethole.*

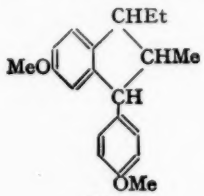
By Wilson Baker and G. F. Flemons.

*iso*Anethole (I), previously known only as an oil, is shown to be a mixture consisting mainly of crystalline (m. p. 40—40·5°) *trans*(?)-*iso*anethole and a smaller amount of liquid *cis*(?)-*iso*anethole. The claim that metanethole (II) exists in two forms, sublimable and non-sublimable, is incorrect.

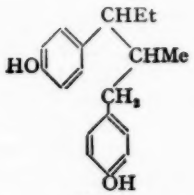
Anethole undergoes dimerisation under the influence of hydrogen chloride to give *iso*anethole, which has been shown by Goodall and Haworth (*J.*, 1930, 2482) to possess the structure (I). These authors oxidised the liquid *iso*anethole to anisic acid and methyl 1-*p*-methoxyphenyl-*n*-propyl ketone, but this experiment leaves in doubt the question, not previously raised, as to whether *iso*anethole is the *cis*- or *trans*- isomeride or a mixture of the two. Formula (I) represents what may be termed the *trans*-form, attention being focussed on the main Ar–C=C–C–Ar chain of the molecule. Optically active forms of *iso*anethole are possible.



(I.)



(II.)



(III.)

Baker and Enderby (*J.*, 1940, 1094) showed that anethole could be dimerised by refluxing in 43% sulphuric acid, giving a mixture of the saturated, crystalline dimeride metanethole (II)

(see below) and *iso*anethole, the latter having the same boiling point and almost the same refractive index as *iso*anethole prepared by the method of Goodall and Haworth. The *iso*anethole was further identified by the oxidative degradation mentioned above, and by catalytic reduction followed by demethylation to give 1 : 3-di-*p*-hydroxyphenyl-2-methylpentane (III), which, after purification, had m. p. 126—127° (see Campbell, Dodds, and Lawson, *Proc. Roy. Soc.*, 1940, *B*, **128**, 253).

trans(?)-iso*Anethole*.—A specimen of *iso*anethole prepared by the sulphuric acid method (Baker and Enderby, *loc. cit.*, p. 1096; the actual specimen is referred to in lines 9 and 10 from bottom) was observed after several months to have begun to crystallise, and, after several years, it had become mainly solid. This solid *iso*anethole was isolated and could be crystallised from methyl alcohol under exactly controlled conditions, the yield being about 60%. *iso*Anethole prepared by the method of Goodall and Haworth was also readily obtained in the solid state, and gave the recrystallised material in 80% yield. This solid iso*anethole*, m. p. 40—40·5°, may be provisionally allotted the *trans*-structure (I), as it apparently possesses a higher melting-point than the other stereoisomeride which has as yet been obtained only as an oil (see below). It may be noted that, for steric reasons, the *trans-iso*anethole (I) might be expected to undergo easier cyclisation to metanethole (II) than the *cis*-isomeride, and metanethole is, in fact, formed more smoothly and in somewhat greater yield from solid *iso*anethole than from the liquid isomer by the action of stannic chloride in chloroform (Baker and Enderby). There is the possibility that *cis*- and *trans-iso*anetholes might yield different stereoisomers of metanethole, but no evidence was obtained that this was the case. Catalytic reduction followed by demethylation readily gave almost pure 1 : 3-di-*p*-hydroxyphenyl-2-methylpentane (III) in 95% yield without crystallisation.

cis(?)-iso*Anethole*.—*iso*Anethole prepared from anethole by the action of hydrogen chloride or sulphuric acid, after isolation of the crystalline *iso*anethole, yields an oil which gives analyses agreeing with those required by a dimeric anethole. Oxidation with potassium permanganate yielded only anisic acid and methyl 1-*p*-methoxyphenyl-*n*-propyl ketone, so that this liquid product must possess the same structure as solid *iso*anethole, and is doubtless a mixture of *cis-iso*anethole and an unknown amount of the solid *trans-iso*anethole. Catalytic reduction resulted in the uptake of one molecule of hydrogen, and subsequent demethylation gave as the only isolable solid the same stereoisomeride of 1 : 3-di-*p*-hydroxyphenyl-2-methylpentane (III) as was given by the solid *iso*anethole, but the yield was not above 45%. A liquid stereoisomeride of (III), of which two racemic forms are possible, is doubtless present in the reaction product.

Metanethole.—Metanethole, m. p. 134°, has been prepared, usually in very small yield, by the action of a variety of acidic reagents on anethole (for references see Baker and Enderby, *loc. cit.*), the most convenient being boiling 43% sulphuric acid, which gives a 25% yield. Yamashita (*J. Chem. Soc. Japan*, 1941, **62**, 1216) has since reported the production of metanethole in unstated yield by the action of iodine upon a toluene solution of anethole, and Bruckner (*Ber.*, 1942, **75**, 2034) records the production of a trace of metanethole while investigating the reaction of anethole with maleic anhydride. Van der Zanden, de Vries, and Dijkstra (*Rec. Trav. chim.*, 1942, **61**, 280) obtained metanethole in under 1% yield by the action of the boron fluoride–diethyl ether complex on methylchavicol (*p*-methoxyallylbenzene, source unstated), and Polak and Hixon (*J. Amer. Pharm. Assoc.*, 1945, **34**, 240) claim the formation of metanethole in 2·2% yield by boiling methylchavicol with " 34% sulphuric acid " according to the directions of Baker and Enderby (this is doubtless an error for " 43% sulphuric acid "). In the latter case, at least, it seems very likely that the metanethole may have been derived from a few per cent. of anethole in the methylchavicol, which was isolated from the steam-volatile oil of " anise hyssop " (*Lophanthus anisatus* Benth). Polak and Hixon also report the spontaneous polymerisation of methylchavicol from " anise hyssop " during 8 months' storage, 11—25% passing into a mixture of *iso*anethole and metanethole. They claim, however, that this metanethole, m. p. 134°, sublimes at 110—120°, and differs therein from the " non-sublimable " metanethole of the same m. p. prepared from anethole by the method of Baker and Enderby or by the action of sulphuric acid upon methylchavicol. It was also recalled that Perrenoud (*Annalen*, 1877, **187**, 68), who prepared metanethole by the action of zinc chloride and superheated steam upon anethole, reported that the product was sublimable at 115—120°, and that Glichitch (*Bull. Soc. chim.*, 1924, **35**, 1160), who prepared metanethole by the action of 90% formic acid on anethole, also described it as sublimable. Polak and Hixon, in an attempt to establish a difference between " sublimable " and " non-sublimable " metanethole, found that a mixture of the two " gave one degree depression after the mixture had been melted, cooled, and pulverised three times ".

We have been unable to detect any difference between metanethole prepared by the methods

of Baker and Enderby, Perrenoud, and Glichitch. All the specimens sublime exceedingly slowly at *ca.* 115—130° in needles at atmospheric pressure, and even under favourable conditions in a vacuum the rate of sublimation remains minute. In the ordinary use of the term, the specimens would scarcely be described as sublimable. When heated more strongly in a small tube, the melt shows a marked tendency to creep rapidly and solidify on the cooler parts of the tube, a phenomenon which might be mistaken for rapid sublimation. That there is no difference between " sublimable " and " non-sublimable " metanethole is completely confirmed by *X*-ray powder photographs, kindly taken by Dr. T. Malkin and Mr. F. I. G. Small in this laboratory; they report as follows.

" *X*-Ray powder photographs of all three specimens were taken, using a Phillips Metalex tube (CuK_α) running at 10 m.A. With a specimen-to-camera distance of 6 cm., excellent photographs were obtained in half-an-hour. Sixteen lines appeared on the three photographs, identical in intensity and position. The strongest eight lines correspond to spacings of 3·28, 3·57, 3·84, 4·31, 5·12, 5·44, 5·80, and 7·89 A. There can, therefore, be little doubt as to identity of all three specimens."

We are therefore unable to find any difference between " sublimable " and " non-sublimable " metanethole, but we have not been able to examine the material prepared by Polak and Hixon from " anise hyssop ".

The structure (II) of metanethole established by Baker and Enderby has received confirmation in the work of Müller and Richl (*Ber.*, 1943, **76**, 1119), and it is of interest that di*iso*eugenol has now been allotted a precisely similar structure (Cartwright and Haworth, *J.*, 1947, 948) in place of its original formulation as a 9 : 10-dihydroanthracene. Four racemic stereoisomeric forms of metanethole (II) should be capable of existence.

Experimental.

Isolation of Solid trans(?)-iso*Anethole* (I).—(*a*) Part of the analytically pure specimen of *iso*anethole prepared by Baker and Enderby (*loc. cit.*, p. 1096) (50 g.) which was finally of the consistency of well-crystallised honey, was pressed on porous earthenware (see below) and yielded a white, crystalline powder (35·5 g.), melting at 38—40° to a turbid melt which became clear at 45°. (*b*) *iso*Anethole prepared by the method of Goodall and Haworth, b. p. 186—191°/0·5 mm., crystallised at once after distillation without intentional seeding to a hard mass, m. p. 28—35°, which could not be plated. This material (35·5 g.) and that described under (*a*) were separately treated as follows. The solid *iso*anethole was dissolved in warm methyl alcohol (280 c.c.), cooled, a very little more methyl alcohol added so that the solution remained clear at 20° but was slightly cloudy at 19°, seeded at 20°, and allowed to crystallise at room temperature with occasional gentle stirring for several hours. Further separation of crystals occurred on keeping overnight in the ice-chest, and the product was then collected, washed with a little ice-cold methyl alcohol and dried. Material from (*a*) (31·3 g.) had m. p. 39—40°, becoming clear at *ca.* 45°; no further crystalline material was obtained from the mother liquors. Material from (*b*) (23·3 g.) had m. p. 39—40°, the melt being almost clear, and more solid (5·1 g.) was obtained from the mother-liquor by concentration and crystallisation as before. Further similar recrystallisations of the *iso*anethole from (*a*) did not materially alter its properties; the turbidity of the melt is probably due to a persistent trace of metanethole. A specimen of *iso*anethole of satisfactory purity was obtained from (*b*) by dissolving the once crystallised product (23·3 g.) in methyl alcohol (solution clear at 20°, turbid at 19°), collecting the solid which separated at room temperature (14·7 g.), and cooling the mother-liquor to 0°; a product (5·3 g.) had m. p. 40—40·5°, the melt being quite clear. No depression of the melting point was observed when specimens from the two sources were mixed.

trans(?)-iso*Anethole* forms thin, colourless plates, having in the supercooled state $n_D^{20°}$ 1·5830 (Found : C, 81·1; H, 8·2. $C_{20}H_{24}O_2$ requires C, 81·0; H, 8·2%).

Liquid cis(?)-iso*Anethole*.—(*a*) The oily *iso*anethole contained in the porous plate (above) was extracted and distilled twice under diminished pressure, giving a very pale yellow oil (12·5 g.), b. p. 174°/0·05 mm., $n_D^{20°}$ 1·5764 (Found : C, 81·0; H, 8·3. Calc. for $C_{20}H_{24}O_2$: C, 81·0; H, 8·2%). (*b*) The methyl alcoholic mother-liquors from the crystallisation of the solid *iso*anethole prepared by the method of Goodall and Haworth [section (*b*) above] were distilled, giving an oil, b. p. 174—176°/0·05 mm., $n_D^{20°}$ 1·5770. Neither specimen could be induced to crystallise, and both, when oxidised by potassium permanganate in acetone, gave anisic acid, m. p. 184°, and methyl 1-*p*-methoxyphenyl-*n*-propyl ketone (characterised as the semicarbazone, thin, rhombic plates from alcohol, m. p. 190—191°; Goodall and Haworth record m. p. 189°) in similar yields.

Conversion of Solid and Liquid iso*Anetholes into Metanethole* (II).—Each *iso*anethole (5 g.) was treated with anhydrous stannic chloride in chloroform solution, and the metanethole was isolated, as described by Baker and Enderby. The solid *iso*anethole readily gave metanethole (0·5 g.), m. p. 134°. The liquid *iso*anethole gave at first a less pure product yielding finally metanethole (0·4 g.), m. p. 134°. No other crystalline material could be isolated from either.

Conversion of Solid and Liquid iso*Anetholes into* 1 : 3-*Di*-p-*hydroxyphenyl*-2-*methylpentane* (III).—(*a*) Solid *iso*anethole (6·0 g.) was reduced (10 minutes) in alcohol (25 c.c.) with hydrogen in presence of a 2% palladium–strontium carbonate catalyst. The product was isolated and refluxed for 5 hours with glacial acetic acid (25 c.c.) and hydrobromic acid (25 c.c.; *d*, 1·47). Addition of water then precipitated (III) as an oil which rapidly solidified to a colourless solid (5·2 g.), m. p. 124—127°, recrystallisation of which from chloroform gave stout prisms, m. p. 129° (Campbell, Dodds, and Lawson, *loc. cit.*, give m. p.

128° from *cyclo*hexane). (*b*) Similar treatment of liquid *iso*anethole (6·0 g.) gave a brown oil of low melting point (5·0 g.) which after one crystallisation from chloroform gave material, m. p. 122—128° (2·6 g.). Further crystallisation gave the pure compound, m. p. 129°. No other solid material could be isolated from the mother-liquors.

The authors' thanks are due to the Colston Research Society and Imperial Chemical Industries Limited for grants which have defrayed part of the cost of this research, and to Mr. L. J. Breddy for the preparation of specimens of metanethole by the methods of Perrenoud and Glichitch.

THE UNIVERSITY, BRISTOL. [*Received, January 16th*, 1948.]

NOTES.

Composition, Pressure, and Temperature Relationships in Binary Azeotropic Systems. By O. REDLICH.

THE recent paper by Coulson and Herington (*J.*, 1947, 597; see also *Nature*, 1946, **158**, 198) follows the discussion of the azeotropic equilibrium presented by the author and the late Professor P. W. Schutz (*J. Amer. Chem. Soc.*, 1944, **66**, 1007) in various steps, namely, in the enumeration of the relationships between composition, pressure, and temperature, in the procedure of deriving these relationships, and in the application to available data regarding the azeotropic temperature range and Wrewski's rule. There are, however, differences in three points:

(1) The quantities $(\partial a/\partial T)_{N_2}$ and $(\partial a/\partial N_2)_T$ in Coulson and Herington's eqn. (4) are undefined as long as no instruction is given as to how the pressure is to be varied in the calculation of these derivatives. In view of the interdependence of the variables the pressure cannot be kept constant, but it is to be considered as a function either of N_2 or, more conveniently, of T. A simple calculation shows that the expression $[\partial(\ln p_1/p_2)/\partial T]_{N_2}$ in eqn. (8) is not to be derived at constant pressure, as we should expect without further instruction, but with the pressure varying according to the shift of the azeotropic equilibrium. Consequently this term must not be replaced by $(\bar{H}_1 - \bar{H}_2)/RT^2$ as suggested by Coulson and Herington but by $(\bar{H}_1 - \bar{H}_2 + v\Delta H)/RT^2$ in precise agreement with eqn. (10) of our paper. This equation follows in a straightforward way from our eqn. (4) which expresses a total differentiation in precise terms. The belief that three independent variables appear in our eqn. (4) rests on a misunderstanding.

The term $v\Delta H$ is quite frequently *not* negligible compared with $\bar{H}_1 - \bar{H}_2$. It may be even of the same order of magnitude, for instance, if both components approximately satisfy Trouton's rule or deviate from this rule by approximately equal amounts.

(2) Coulson and Herington suggest a linear relationship between T and N_2 for determining the azeotropic temperature range, and represent data for aqueous solution of hydrogen chloride by a straight line in their Fig. 1. They overlook our strict conclusion that systems with a dissociating component have an infinite azeotropic temperature range. A linear relationship is inconsistent with this conclusion.

(3) The fact that the N_2–T curves can be approximated by straight lines even for not "strictly regular" solutions results in the case of hydrogen chloride solutions simply from the smallness of the composition range ($0{\cdot}107 < N_2 < 0{\cdot}131$). For ethyl acetate–ethanol a systematic deviation is noticeable; it would be more conspicuous if the point at 0° were added (see Fig. 1 of our paper). No conclusion can be drawn from the fact that data in a limited range can be imperfectly represented by a relationship with two coefficients *derived from the same data*. In our discussion, on the other hand, the results for hydrochloric acid were derived from *entirely different* data (activity coefficients, etc.).

No objection is raised against the simplification of general thermodynamic relationships by justified assumptions. The danger of oversimplification is sufficiently illustrated by the example of the hydrogen chloride solutions. In a case like this significant results cannot be obtained without somewhat laborious calculations. The legitimate range of application of the "strictly regular" solution is so narrow that the general relationships cannot be dispensed with. The special case was only briefly mentioned in our discussion because all essential aspects were fully discussed by Kireev and, in principle, even earlier by Herzfeld and Heitler (*Z. Elektrochem.*, 1925, **31**, 536).

A few decades ago quite a few physical chemists believed that general thermodynamic relationships are "formal" and not useful in practical applications because at that time convenient methods were developed only for the perfect solution. We should avoid a similar restriction to "strictly regular" solutions.—BERKELEY, CALIFORNIA. [*Received, September 19th*, 1947.]

Remarks on Redlich's Note on Composition, Pressure, and Temperature Relationships in Binary Azeotropic Systems. By E. A. COULSON and E. F. G. HERINGTON.

THROUGH the courtesy of Dr. Redlich we have been able to see a copy of the preceding Note. Our critical review of prior work led us to extend the discussion to include "strictly regular" solutions which allowed us to obtain explicit relationships between composition and pressure and temperature. This is beyond the scope of Redlich and Schutz's treatment (*loc. cit.*) even if the latter had been formally accurate.

The first point is the central issue between us. The pressure is precisely specified in our treatment as being throughout the total pressure of the vapour phase, so that the differentials to which Redlich draws attention are completely defined. Redlich and Schutz's equations (4) and (9) cannot be reconciled with our corresponding equations (4) and (8). The difference is fundamental. Redlich now disputes that three independent variables appear in his equation (4), thus tacitly admitting that there should not be more than two independent variables, but there can, we think, be no question that three independent

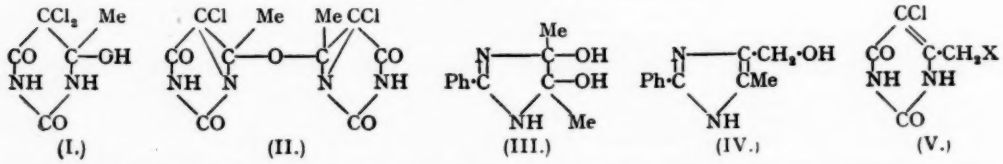
variables have in fact been employed by Redlich. Moreover, no explanation has been furnished, even now, why the phase rule is ignored in this way.

The second and the third point are of minor interest. They raise matters upon which opinions may legitimately differ and do not seem to warrant further discussion at this stage.—CHEMICAL RESEARCH LABORATORY, TEDDINGTON, MIDDLESEX. [*Received, October 7th*, 1947.]

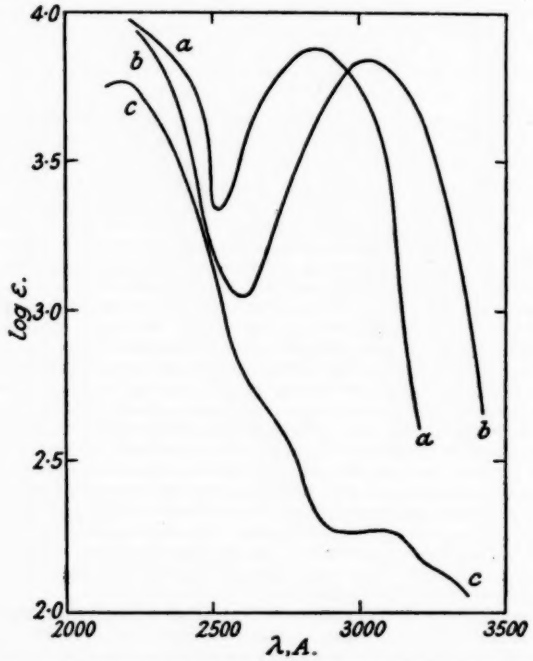
The Action of Hydrochloric Acid on 5 : 5-*Dichloro*-6-*hydroxy*-6-*methyl*-5 : 6-*dihydrouracil.*

By J. W. CORNFORTH and H. T. HUANG.

JOHNSON (*J. Amer. Chem. Soc.*, 1943, **65**, 1220; 1944, **66**, 146) has reported that 5 : 5-dichloro-6-hydroxy-6-methyl-5 : 6-dihydrouracil (I) on treatment with hot hydrochloric acid or acetic anhydride gave a substance to which he ascribed the " bicyclouracil " structure (II).



The action of hydrochloric acid on 4 : 5-dihydroxy-2-phenyl-4 : 5-dimethyl-4 : 5-dihydroglyoxaline (III) has been shown by us (this vol., p. 731) to give 2-phenyl-5-methyl-4-hydroxymethylglyoxaline (IV). The analogy between (I) and (III) prompted a repetition of Johnson's experiment: the



Ultra-violet absorption (*in* N/20 NaOH) *of* (a) 5-*chloro*-6-*methyluracil*, (b) 5-*chloro*-6-*chloromethyluracil*, (c) 5 : 5-*dichloro*-6-*hydroxy*-6-*methyl*-5 : 6-*dihydrouracil.*

dihydrouracil (2 g.: Behrend, *Annalen*, 1886, **236**, 59) was refluxed with concentrated hydrochloric acid (20, 30, 40, 50 c.c.) for periods of 2—12 hours. The product (1·2—1·5 g.) was the same in every case; it crystallised from hot water, dilute hydrochloric acid, or glacial acetic acid in shining prisms, m. p. 270—275° (somewhat variable) with decomposition after decrepitation at 220° and darkening from 250°. The m. p. is that given by Johnson but a different composition was found on analysis (Found, after drying at 100—110°: C, 31·1, 31·2, 30·7, 30·9; H, 2·4, 2·1, 2·3, 2·2; N, 14·7; Cl, 36·3, 36·3, 35·9, 36·6, 36·4. $C_5H_4O_2N_2Cl_2$ requires C, 30·8, H, 2·1; N, 14·4; Cl, 36·4%). The ultra-violet absorption spectrum showed λ max. 3025 A. (log ϵ, 3·83), λ min. 2600 A. (log ϵ, 3·05). The presence of a true uracil ring was established by comparison with the spectra of 5-chloro-6-methyluracil (V; X = H; Behrend, *loc. cit.*), which had λ max. 2840 A. (log ϵ, 3·87), λ min. 2510 A. (log ϵ, 3·34), and of the dihydrouracil (I), which showed only end absorption. The substance is therefore 5-*chloro*-6-*chloromethyluracil* (V; X = Cl), and is evidently produced from (I) by dehydration and anionotropic change as postulated (*loc. cit.*) for the conversion of (III) into (IV). The same substance (V; X = Cl) was formed in poor yield by the action of acetic

anhydride on (I). When the chloromethyluracil (V; X = Cl) was refluxed in acetic acid for 4 hours with an equal weight of zinc dust, 5-chloro-6-methyluracil (V; X = H) was formed, m. p. 330—332° (decomp.) after crystallisation from water (Found: C, 37·8; H, 3·2; N, 17·0; Cl, 21·4. Calc. for $C_5H_5O_2N_2Cl$: C, 37·4; H, 3·1; N, 17·4; Cl, 22·1%). The chloromethyluracil (V; X = Cl) dissolved in dilute aqueous sodium hydroxide without decomposition, though, on keeping, chloride ion was slowly liberated; it was recovered unchanged (Found: Cl, 36·7%) after being kept for a fortnight with nitric acid (*d* 1·42) at room temperature. No product having the composition of (II) could be obtained by treating (I) with hydrochloric acid and no explanation of Johnson's results can be offered.

We thank the British Council for enabling H. T. H. to take part in this work.—Dyson Perrins Laboratory, Oxford University, and National Institute for Medical Research, Hampstead. [*Received, December 28th*, 1947.]

The Action of Amines upon Esters. Part II. By Harry Irving and Howard I. Fuller.

It has now been confirmed that the formation of amines (III; X = H, alkyl, aryl, NHAr, etc.) rather than the amides expected by the action of ammonia and its substitution products upon certain esters (I; R = Ac) results from the addition of these amines to the double bond of the nitro-olefin (II) postulated as a reaction intermediate (Irving, *J.*, 1936, 797).*

$$\underset{\text{(I.)}}{CCl_3\cdot CH(OR)\cdot CH_2\cdot NO_2} \xrightarrow[-\ ROH]{(NH_4X)} \underset{\text{(II.)}}{CCl_3\cdot CH{:}CH\cdot NO_2} \xrightarrow{+\ NH_4X} \underset{\text{(III.)}}{CCl_3\cdot CH(NHX)\cdot CH_2\cdot NO_2}$$

Though elimination of acetic acid from the ester (I; R = Ac) by refluxing in ethereal solution with potassium hydrogen carbonate (cf. Schmidt and Rutz, *Ber.*, 1928, **61**, 2142) did not prove a satisfactory method of preparation, (II) was readily obtained by distilling the nitro-alcohol (I; R = H; 1 mol.) with phosphoric oxide (3 mols.) under reduced pressure (45 mm., oil-bath at 150°). 3 : 3 : 3-*Trichloro*-1-*nitropropene* (II) is a highly lachrymatory, pale yellow, oily liquid, b. p. 80—81°/13 mm., insoluble in water, but miscible with organic solvents (Found: C, 19·5; H, 1·3; N, 6·7; Cl, 55·8. $C_3H_2O_2NCl_3$ requires C, 18·9; H, 1·05; N, 7·35; Cl, 55·9%). It did not react with water during 2 months, or decolourise bromine within 48 hours but, as expected, it reacted exothermically with an alcoholic solution of phenylhydrazine (1 equiv.) to give a practically quantitative yield of 1 : 1 : 1-trichloro-3-nitro-2-phenylhydrazinopropane (III; X = NHPh), m. p. 119—120° from alcohol, identical with an authentic specimen prepared from phenylhydrazine and the nitro-ester (I; R = Ac); *p*-toluidine and (II) reacted in chloroform to give 1 : 1 : 1-trichloro-3-nitro-2-(*p*-toluidino)propane, which crystallised as pale yellow rhombs, m. p. 62° from petrol (b. p. 40—60°) or alcohol (cf. Chattaway, *J.*, 1936, 356). The nitro-olefin did not react with phenylhydrazine hydrochloride.

In ethyl alcohol at 20° the reaction between phenylhydrazine (0·046, 0·048, and 0·047 g.-mol./l.) and 1 : 1 : 1-trichloro-3-nitro-2-acetoxypropane (I; R = Ac; 0·075, 0·15, and 0·30 g.-mol./l.) was 50% completed in 60, 23, and 13 minutes, respectively. Under comparable conditions the ester did not react with phenylhydrazine hydrochloride and only slowly with phenylhydrazine acetate. The reaction with phenylhydrazine itself was found to be strongly catalysed by various bases; it could be stopped immediately by adding 2N-hydrochloric acid, and the rate determined by estimating excess phenylhydrazine iodometrically (Meyer, *J. pr. Chem.*, 1887, **36**, 115; as modified by Ardagh, *J. Amer. Chem. Soc.*, 1932, **54**, 721).—The Inorganic Chemistry Laboratory, Oxford University. [*Received, December 31st*, 1947.]

Preparation of Mannose. By F. Smith.

Hitherto the best source of mannose has been the vegetable ivory nut (Reiss, *Ber.*, 1889, **22**, 609). The preparation of mannose from ivory nut mannan worked out by Hudson (*Org. Synth.*, Coll. Vol. 1, 371) involves a lengthy hydrolysis of the mannan using considerable amounts of sulphuric acid. The mannose is purified by the formation of α-methylmannoside which is then reconverted into mannose in the usual way (Hudson and Jackson, *J. Amer. Chem. Soc.*, 1934, **56**, 958). Instead of ivory nut mannan which is relatively stable to acids, it is believed that carob gum, from the carob bean *Ceratonia siliqua*, a galactomannan containing 80% mannose, is a better source of mannose. This polysaccharide undergoes hydrolysis with ease, and high yields of α-methylmannoside can be obtained from it.

Experimental.—Carob gum (sometimes called St. John's bread), from the carob bean, *Ceratonia siliqua* (100 g.), is heated for 9 hours on the boiling water-bath with 0·5N-sulphuric acid (500 c.c.). After removal of a flocculent precipitate on the centrifuge, the solution ($[\alpha]_D$ + 22·5°) is neutralised with a solution of barium hydroxide, treated with a little charcoal, and filtered hot. Evaporation of the filtrate to dryness under reduced pressure gives a glassy residue which is then boiled for 6 hours with 3% methyl-alcoholic hydrogen chloride (250 c.c.). The solution is concentrated under reduced pressure to half volume and cooled, and the crystalline α-methylmannoside is filtered off, washed with cold methyl alcohol, and dried (yield, 44 g.). A further 5—6 g. can be obtained from the mother liquors. After crystallisation from water the α-methylmannopyranoside shows m. p. 195°, $[\alpha]_D^{18°}$ + 80° in water (*c*, 1·0).

Hydrolysis of the α-methylmannoside with N-sulphuric acid (5 parts) on a boiling water-bath until

* After this paper had been submitted, Heath and Rose (*J.*, 1947, 1487) showed that the addition of amines to nitro-olefins is a general reaction, but, although noting that the latter can advantageously be replaced by esters of the corresponding nitro-alcohols, they do not comment on the mechanisms of these "abnormal" reactions (cf. Irving, *loc. cit.*).

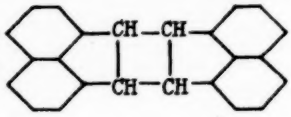
the rotation is constant gives rise to mannose, which can be isolated and crystallised in the usual manner (cf. Hudson and Jackson, *loc. cit.*), m. p. 127—128°, $[\alpha]_D^{15°}$ + 14° equilibrium value in water (*c*, 2).—THE UNIVERSITY, MINNEAPOLIS, MINNESOTA, U.S.A. THE UNIVERSITY, EDGBASTON, BIRMINGHAM 15, ENGLAND. [*Received, November 26th*, 1947.]

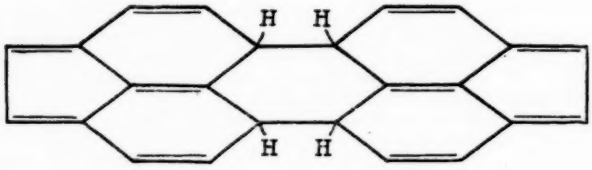
The Dimerisation of Acenaphthylene. By V. A. CRAWFORD and C. A. COULSON.

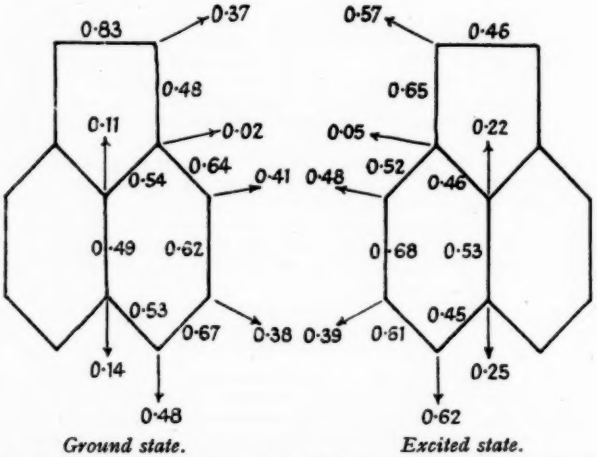
IN the presence of ultraviolet light the acenaphthylene hydrocarbon (I) forms a colourless dimer (II). The nature and quantum efficiency of this process have recently been discussed by Bowen and Marsh (*J.*, 1947, 109). It seems probable that the mechanism is not a simple " collisional " one, but depends on the existence of van der Waals complexes in the solution.

In the case of a relatively non-polar molecule such as acenaphthylene, the formation of these complexes is probably facilitated by the presence of a high " free valence " at the reacting carbon atoms (Coulson,

(I.)

(II.) 

(III.) 



Ground state. *Excited state.*

Bond orders and free valence in the ground and the excited state. For comparison, bond order in benzene is 0·67 and free valence is 0·35. In ethylene, they are 1·00 and 0·68, respectively.

Trans. Faraday Soc., to appear). For that reason, and in order to throw further light on the process, we have calculated the bond orders and free valences in this molecule, both in its ground state and in the lowest excited state. This latter is presumably the one into which the molecule is thrown by the absorption of the mercury 4360, 4050 and 3650 A. radiation used by Bowen and Marsh. We have adopted the standard molecular-orbital technique (see, *e.g.*, Coulson, *Quart. Reviews*, 1947, **1**, 144) for calculating bond orders and interpreting the lowest excited level. In these calculations we have neglected, as is usual, the overlap integral between adjacent carbon π orbitals.

The numerical results for the two electronic states are shown in the diagram. The figures along a bond denote the mobile bond order p ($100p$ may be called percentage double-bond character), and the figures at the arrowheads denote the free valence at the appropriate carbon atom. As the molecule is symmetrical, bond orders and free valences on the one side are equal to those on the other side.

These figures show that the effect of excitation is to diminish the bond order of the ethylene-type linkage much more than that of any other part of the molecule. It is approximately, though not entirely, true to say that the excitation resides largely in this region. As a result, the free valence at each end of this bond is considerably enhanced, this increase much exceeding the increase at any other part of the

molecule. It is not in any way surprising, therefore, that the dimerisation takes place at this ethylene-type linkage, and that it is greatly facilitated by ultra-violet absorption. If our interpretation is correct, we have a good illustration of the fact that a high bond order is not, *per se*, an advantage in promoting reactivity of a homolytic kind. Rather is it true to say that the reactivity is increased when, as a result of electronic excitation, the high bond order has been sacrificed to create an enhanced free valence.

However, if we accept this large free valence at the outer link as an explanation of the dimerisation there, we have still to understand why no reaction takes place at the opposite vertices (4, 5 —) of the naphthalene nucleus, where the calculated free valence is also large. It seems fairly well established that dimerisation does not take place at these centres, even though, in the presence of a catalyst, naphthalene itself does react slightly in this manner to form dinaphthyl (Moureu, Chovin, and Rivoal, *Compt. rend.*, 1946, **223**, 951). The explanation is quite simple. For if we suppose the dimerisation to take place in such a way that (III) is formed, then, as the bond diagram shows, we are left with a molecule in which only quinonoid structures can be drawn, so that the aromatic character of both naphthalene nuclei has been destroyed. Indeed a system such as (III) must be much less favoured energetically than one such as (II) in which the resonance in both naphthalene nuclei is retained. This example shows that free valence, by itself, is not a sufficient guide to reactivity, even of homolytic type. It requires at least to be supplemented by a discussion of the stability of the final products.—Department of Theoretical Physics, King's College, London. [*Received, December 23rd*, 1947.]

Fluorides of the Natural Radioactive Elements. By H. J. Emeléus, A. G. Maddock, G. L. Miles, and A. G. Sharpe.

Bromine trifluoride reacts rapidly and quantitatively at temperatures below its boiling point with most uranium compounds and forms the volatile hexafluoride. It has been established that under the same conditions, none of the other naturally occurring elements of atomic number greater than 80 (apart from radon) volatilises quantitatively with this reagent. This reaction is thus useful in the analysis of mixtures of radioactive materials and in the final stages of the preparation of large uranium-X_1 sources. Very thin uranium-X_1 sources have been prepared by solvent extraction of the bulk of the uranium in a sample of uranyl nitrate containing uranium decay products, followed by fluorination of the residue with bromine trifluoride. The evidence presented in no way excludes the formation of a volatile fluoride by an element such as polonium by other methods, *e.g.*, direct fluorination.

Experimental.—The elements other than uranium which might conceivably form volatile fluorides on treatment with bromine trifluoride are thallium, lead, bismuth, polonium, thorium, and protoactinium. As far as possible each of these was examined both by macro- and by tracer procedures. In the first case a weighed quantity of a compound of the element was treated with excess of liquid bromine trifluoride in a silica vessel attached by a train of traps to a vacuum apparatus. After allowing time for reaction, the excess of bromine trifluoride was pumped off and condensed. Finally, the reaction vessel was warmed to 120° at a pressure of less than 0·01 mm. The distillates were collected and analysed for the element under investigation.

No visible residue remained when 200-mg. samples of uranium metal, UO_2, UO_3, or U_3O_8 were treated. Gravimetric and colorimetric analysis of the distillate showed that the uranium had been volatilised quantitatively. No volatile products were obtained from thallium oxides, lead chloride, lead fluoride, or thorium oxide. The condensate obtained by treating bismuth trioxide gave a detectable reaction with hydrogen sulphide.

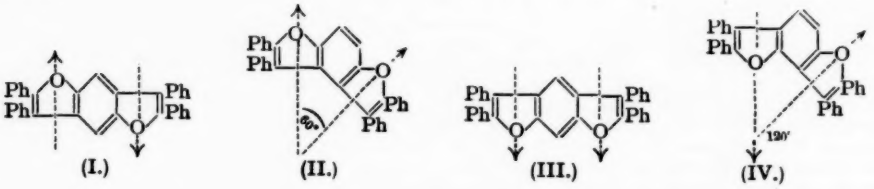
The tracer experiments were carried out by depositing the active material on glass or metal-foil discs, such as were used for counting. The activity of the deposit on the disc was measured before and after treatment with bromine trifluoride. The activity of the condensate was determined when that of the original deposit was decreased by the fluorination.

Three 100-mg. samples of U_3O_8 retained an average of 0·04% ± 0·01% of their α-activity after a short treatment with bromine trifluoride. The condensate, after correction for the uranium-X_1 grown since the time of distillation, possessed no activity. Thus uranium isotopes are volatile and those of thorium non-volatile under this treatment. With glass discs, mechanical losses prevented efficient recovery of the uranium-X_1, but with metal discs more than 90% of the β-activity remained on the discs. Rapid examination of the β-activity of the residues from the uranium oxide fluorination proved that the short-lived uranium-X_2 is also non-volatile under these conditions. This was confirmed by treatment of four foils supporting carrier-free ^{233}Pa. In each case the loss of activity by the foil was less than the counting error (± 1·5%). Similar results were obtained when using natural ^{231}Pa. Duplicate experiments with foils carrying thorium oxide containing mesothorium (an isotope of Ra) and mesothorium-2 (an isotope of Ac) showed no significant loss in activity.

A series of nine polonium foils gave a mean loss of 4·5% ± 1·0% on fluorination, but it was found that the same loss was experienced in blank experiments in which bromine trifluoride was omitted. It must therefore be attributed to the pseudo-volatility or recoil effect investigated by Lawson (*Nature*, 1919, **102**, 465). This is supported by the observation that less than 0·01% of the polonium reached the condensation trap. Four experiments with a mixture of Ra-*D*, Ra-*E*, and Ra-*F* on a lead oxide carrier showed that about 6% of the more penetrating β-active body (Ra-*E*) volatilised. Examination of the condensate showed the presence of 5% of the Ra-*E* originally present in the sample. This isotope of bismuth presumably volatilised as the pentafluoride, which has a sublimation pressure of 1 atm. at 550° (von Wartenburg, *Z. anorg. Chem.*, 1940, **244**, 337), as was indicated by the macro-experiments already described.—University Chemical Laboratory, Cambridge. [*Received, January 15th*, 1948.]

The Condensation of Benzoin with Quinol or Resorcinol. By R. J. W. Le Fèvre, C. R. Taylor, and R. N. Whittem.

Japp and Meldrum (*J.*, 1899, **75**, 1035), by the condensation of benzoin with quinol or with resorcinol in 73% sulphuric acid obtained "para- or meta-benzotetraphenyldifurfuran," respectively, but made no decision between the obvious alternative formulæ, (I) or (II), (III) or (IV) (see Beilstein, "Handbuch," XIX, 62):



Such ambiguities should be resolvable by dipole-moment measurements since the molecular resultants to be expected are, for (I) *ca.* zero, for (II) *ca.* $\sqrt{3}\mu$, for (III) *ca.* 2μ, and for (IV) *ca.* μ, where μ is of the order of those observed for furan (0·63 D., Hunter and Partington, *J.*, 1931, 2062; 0·71 D., Smyth and Walls, *J. Amer. Chem. Soc.*, 1932, **54**, 3230), coumarone (0·79 D., Syrkin and Schott-Lvova, *J. Physical Chem. U.S.S.R.*, 1938, **12**, 479), and diphenylene oxide (0·88 D., Bretscher, *Helv. Physica. Acta*, 1929, **2**, 257), in benzene solutions.

We find, in fact, that in this solvent the quinol derivative has $\mu < 0{\cdot}5$ D., while that from resorcinol has $\mu = 1{\cdot}65$ D. It should be noted, however, (*a*) that the structure (I) has features liable to cause an anomalous solvation moment (Jenkins, *J.*, 1936, 910; Bauer, *J. Chem. Physics*, 1936, **4**, 458; Frank and Sutton, *Trans. Faraday Soc.*, 1937, **33**, 1307; cf., however, Coop and Sutton, *J.*, 1938, 1269) which might easily account for an "apparent" μ of 0·2 or 0·3 D., and (*b*) that in the calculation from the observed 5 c.c. excess of total polarisation over the molecular refraction for Na light, the atomic polarisation (which, while not additive, often increases with the number of atoms in a molecule, cf. Sugden, *Trans. Faraday Soc.*, 1934, **30**, 734; Coop and Sutton, *loc. cit.*) has not been fully subtracted. If, following the common convention, we were to take the distortion polarisation as $1{\cdot}05 \times [R_L]_D$ the figure obtained, 159·6 c.c., would actually exceed our experimental result.

We conclude therefore that (I) and (III) are indicated as the correct formulæ.

Chemical Evidence.—These condensations have been studied also by Dischendorfer (*Sitzungsber. Akad. Wiss. Wien*, 1933, **142**, 69; *Monatsh.*, 1933, **62**, 263; 1935, **66**, 201) who, by chromic acid oxidation of the chief products in acetic acid, isolated the dibenzoates of 2 : 5-dihydroxy-1 : 4-dibenzoyl- and 2 : 4-dihydroxy-1 : 5-dibenzoyl-benzene, respectively (cf. Desai and Radha, *Proc. Indian Acad. Sci.*, 1940, **12**, *A*, 46). Such degradations are in accord with the conclusion reached from the present measurements.

Material and Apparatus.—The condensations were effected by the procedure described by Dischendorfer or Japp and Meldrum (*loc. cit.*), followed by recrystallisation from hot acetic acid (since the resorcinol derivative separated from benzene with solvent of crystallisation). The m. p.s observed were: resorcinol product, 223° (217—219°, J. and M.; 221—222°, D.); quinol product, 280—281° (278°, J. and M.; 281°, D.).

The apparatus used is described by Calderbank and Le Fèvre (this vol., p. 1950) except that for the present work a dielectric cell constructed of concentric brass cylinders sealed into an annular glass envelope (compare the description given in *Trans. Faraday Soc.*, 1947, **43**, 377) replaced the usual silvered Sayce–Briscoe condenser.

The necessary experimental data are set out below, followed by the calculation of results, under headings explained previously (*J.*, 1937, 1805):

$100\,\omega_1$.	$\epsilon_{25°}$.	$d_4^{25°}$.	$a\epsilon_2$.	β.	$100\,\omega_1$.	$\epsilon_{25°}$.	$d_4^{25°}$.	$a\epsilon_2$.	β.
0	2·2725	0·87378	—	—	0	2·2725	0·87378	—	—
	"p-*Benzotetraphenyldifurfuran*."					"m-*Benzotetraphenyldifurfuran*."			
0·2452	2·2740	0·87447	0·612	0·322	0·3280	2·2762	0·87464	1·128	0·300
0·2824	2·2742	0·87462	0·602	0·343	0·6232	2·2795	0·87540	1·123	0·298
0·2922	2·2742	0·87464	0·582	0·337	1·174	2·2858	0·87689	1·133	0·303

Substance.	Mean $a\epsilon_2$.	Mean β.	$_\infty P_1$.	$[R_L]_D$.*	μ, D.
"*p*-Benzotetraphenyldifurfuran"	0·599	0·334	156·9	151·6	0·51
"*m*-Benzotetraphenyldifurfuran"	1·128	0·300	208·3	151·6	1·65

* Calc. from: $2 \times R_{\text{stilbene}}$ (Chilesotti, *Gazzetta*, 1900, **30**, 153) $+ 1 \times R_{\text{benzene}} + 2 \times E_{\text{ether oxygen}} - 8 \times R_H = 130{\cdot}9 + 26{\cdot}2 + 3{\cdot}3 - 8{\cdot}8 = 151{\cdot}6$ c.c.

The standard variable condenser used was originally provided by the Chemical Society Research Fund and grateful acknowledgment thereof is recorded.—University of Sydney, N.S.W., Australia.
[*Received, January 1st*, 1948.]

Some Tri- and Tetra-nitro-4-methyldiphenylamines. By A. F. CHILDS and S. G. P. PLANT.

THE only reference in the literature to a tetranitro-derivative of 4-methyldiphenylamine relates to a compound, m. p. 219°, obtained by Reverdin and Crépieux (*Ber.*, 1903, **36**, 29; *Bull. Soc. chim.*, 1903, **29**, 235) by the nitration of 2′ : 4′-dinitro-4-methyldiphenylamine. Its constitution was not established, and its composition was determined only by a nitrogen determination. It has now been found that the product of the reaction carried out under conditions similar to those used by these authors is 2 : 2′ : 4′-trinitro-4-methyldiphenylamine, m. p. 221°, identified by synthesis from 1-chloro-2 : 4-dinitrobenzene and 3-nitro-*p*-toluidine. 3 : 2′ : 4′-Trinitro-4-methyldiphenylamine, m. p. 207°, has been prepared, for comparison, from 1-chloro-2 : 4-dinitrobenzene and 2-nitro-*p*-toluidine. Further nitration of the 2 : 2′ : 4′-trinitro-compound under more vigorous conditions gave 2 : 6 : 2′ : 4′-tetranitro-4-methyldiphenylamine, m. p. 169°, the constitution of which followed from the fact that it was also obtained by the nitration of 2 : 6-dinitro-4-methyldiphenylamine. 2 : 2′ : 4′ : 6′-Tetranitro-4-methyldiphenylamine has been made, for comparison, from picryl chloride and 3-nitro-*p*-toluidine.

2 : 2′ : 4′-*Trinitro-4-methyldiphenylamine.*—(*a*) When 2′ : 4′-dinitro-4-methyldiphenylamine (7·5 g., prepared from 1-chloro-2 : 4-dinitrobenzene and *p*-toluidine as described by Reitzenstein *J. pr. Chem.*, 1903, **68**, 251) was heated for an hour on a steam-bath with nitric acid (60 c.c., *d* 1·23), the scarlet needles were converted into an orange-yellow solid. After addition of water, the product (6·8 g.), m. p. 210° (after previous softening), was collected and dried. On crystallisation from ethyl acetate, 2 : 2′ : 4′-*trinitro-4-methyldiphenylamine* was obtained in orange-yellow needles, m. p. 221° (Found : C, 48·8; H, 3·1; N, 17·4. $C_{13}H_{10}O_6N_4$ requires C, 49·1; H, 3·2; N, 17·6%). (*b*) After a mixture of 1-chloro-2 : 4-dinitrobenzene (2 g.), 3-nitro-*p*-toluidine (1·6 g.), and potassium carbonate (1·4 g.) had been heated at 150—180° for 1½ hours, the solid mass was ground with warm dilute hydrochloric acid, dried, and boiled with ethyl acetate containing a little charcoal. When the solution was filtered and cooled, 2 : 2′ : 4′-trinitro-4-methyldiphenylamine, identical (mixed m. p.) with the product described above, separated.

3 : 2′ : 4′-*Trinitro-4-methyldiphenylamine.*—A mixture of 1-chloro-2 : 4-dinitrobenzene (6 g.), 2-nitro-*p*-toluidine (4·8 g.), and potassium carbonate (4·2 g.) was heated at 150—160° for an hour, and the product, after being washed with warm dilute hydrochloric acid, was crystallised from glacial acetic acid (charcoal). 3 : 2′ : 4′-*Trinitro-4-methyldiphenylamine* was obtained in golden brown plates, m. p. 207° (Found : C, 49·5; H, 3·1; N, 17·5%). This compound is mentioned in a German patent (D.R.-P., 148,113; Friedlaender, " Fortschritte der Teerfarbenfabrikation," **7**, 341), but no properties are given and no details of its preparation except that the starting materials were the same as those now used.

2 : 6 : 2′ : 4′-*Tetranitro-4-methyldiphenylamine.*—(*a*) When 2 : 2′ : 4′-trinitro-4-methyldiphenylamine (1 g.) was heated on a steam-bath with concentrated nitric acid (25 c.c., *d* 1·42), it gradually dissolved during about 5 minutes. The solution was poured into ice–water, and 2 : 6 : 2′ : 4′-*tetranitro-4-methyldiphenylamine* was precipitated. By crystallisation from alcohol, it was obtained in bright yellow needles, m. p. 169° (Found : C, 42·7; H, 2·4; N, 18·9. $C_{13}H_9O_8N_5$ requires C, 43·0; H, 2·5; N, 19·3%). (*b*) 2 : 6-Dinitro-4-methyldiphenylamine (0·5 g., prepared from 3 : 5-dinitro-*p*-cresol as described by Ullmann and Nádai, *Ber.*, 1908, **41**, 1870) was added to nitric acid (15 c.c., *d* 1·42) at 90°, and the solution, after ½ minute, was poured on ice. When the precipitate was crystallised from alcohol, 2 : 6 : 2′ : 4′-tetranitro-4-methyldiphenylamine, identical (mixed m. p.) with the material described above, was obtained in lemon-yellow needles, m. p. 169°. Jackson and Ittner (*Amer. Chem. J.*, 1897, **19**, 1) state that 2 : 6-dinitro-4-methyldiphenylamine is converted by nitric acid (*d* 1·36) into a " yellow substance, probably a nitro compound ", but the product was not examined further.

2 : 2′ : 4′ : 6′-*Tetranitro-4-methyldiphenylamine.*—When a mixture of picryl chloride (2·5 g.) and 3-nitro-*p*-toluidine (1·5 g.) was heated to 160°, a reaction set in accompanied by considerable frothing. After 20 minutes at this temperature, the product was cooled and crystallised from glacial acetic acid. 2 : 2′ : 4′ : 6′-*Tetranitro-4-methyldiphenylamine* separated in golden brown plates, m. p. 217—219° (Found : C, 43·5; H, 2·4; N, 19·5%).

We are indebted to Sir Robert Robinson for his interest in these investigations, and to the Chief Scientific Officer, Ministry of Supply, for permission to publish the work.—DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, January 30th*, 1948.]

Tetrahydrofurans related to Amidone. By WALTER WILSON.

SCHULTZ, ROBB, and SPRAGUE (*J. Amer. Chem. Soc.*, 1947, **69**, 2454) obtained 2-imino-3 : 3-diphenyl-5-methyltetrahydrofuran from propylene oxide, diphenylmethyl cyanide, and potassium *tert.*-butoxide, and refer to unpublished work by Easton, Gardner, and Stevens * in which the same compound was made with sodamide as the condensing agent. The same structure had been assigned independently in these laboratories to the product obtained using sodamide, on the basis of the acid hydrolysis to αα-diphenyl-γ-valerolactone (described by Schultz, Robb, and Sprague, *loc. cit.*) and the experiments appended.

The basic imino-compound gave an *N*-acetyl derivative with acetic anhydride in pyridine. The orientation of the methyl group in αα-diphenyl-γ-valerolactone was established by a synthesis of the lactone by acid hydrolysis of 1-cyano-1 : 1-diphenylbut-2-ene (new preparation using sodamide). The inert amide corresponding to this cyanide was the only product of alkaline hydrolysis. Cautious acidification of a solution of the lactone in alkali afforded a labile solid acid, which reverted to the lactone even on careful drying for analysis.

Ethylmagnesium bromide and the lactone yielded 2-hydroxy-3 : 3-diphenyl-5-methyl-2-ethyltetrahydrofuran, which was converted into the acetate, and dehydrated by methyl- or ethyl-alcoholic hydrogen

* *Added in Proof.*—Details are now available (*J. Amer. Chem. Soc.*, 1947, **69**, 2941). These workers also describe the conversion of cyanobutene into αα-diphenyl-γ-valerolactone.

chloride to 3 : 3-diphenyl-5-methyl-2-ethylidenetetrahydrofuran, without formation of the 2-alkoxytetrahydrofurans (" furanosides ").

The above 2-hydroxytetrahydrofuran is the stable cyclic semi-acetal of a hypothetical hydroxyketone closely related to the new analgesic drug " Amidone ", $Ph_2C(CO{\cdot}C_2H_5){\cdot}CH_2{\cdot}CH(NMe_2){\cdot}CH_3$. The stability of the cyclic form is indicated by the failure to obtain ketonic derivatives, and recalls the rapid formation of αα-diphenyl-γ-valerolactone from the corresponding hydroxy-acid and the isolation of 2-imino-3 : 3-diphenyl-5-methyltetrahydrofuran instead of the expected open-chain hydroxy-cyanide in the condensation of propylene oxide with diphenylmethyl cyanide.

2-*Imino*-3 : 3-*diphenyl*-5-*methyltetrahydrofuran*.—Diphenylmethyl cyanide (77 g.) in dry benzene (300 c.c.) was stirred (3 hours at 40—50°) with sodamide (24 g.). Propylene oxide (23 g.) in benzene (50 c.c.) was added dropwise, and the mixture heated until the colour had changed from deep green to pale yellow. The benzene solution was washed with water. Distillation of the benzene and trituration of the residue with ether–petroleum (b. p. 40—60°) afforded the imino-compound (86 g., 86% yield; m. p. 116—118°, b. p. 155—160°/0·3 mm.). The pure material formed white prisms, m. p. 116·5—118° (Schultz, Robb, and Sprague, *loc. cit.*, give m. p. 114—115°). Warm dilute hydrochloric or lactic acid yielded quantitatively αα-diphenyl-γ-valerolactone, m. p. 115° (Schultz, Robb, and Sprague give m. p. 111—112°).

2-*Acetimido*-3 : 3-*diphenyl*-5-*methyltetrahydrofuran*.—The imino-compound (2·5 g.) and acetic anhydride (1·5 c.c.) were heated at 100° for 1½ hours. The solid (2·8 g.; m. p. 110—112°) obtained on pouring into water was crystallised from benzene–petroleum (b. p. 40—60°), giving white prisms of the *acetimido*-compound, m. p. 114·5—116·5° (Found: N, 4·95. $C_{19}H_{19}O_2N$ requires N, 4·8%).

1-*Cyano*-1 : 1-*diphenylbut*-2-*ene*.—Diphenylmethyl cyanide (28 g.), sodamide (7·0 g.), and benzene (125 c.c.) were stirred at 40° for 1½ hours, then allyl bromide (17·6 g.) in benzene (25 c.c.) was added dropwise. The reaction was completed by heating to 90°, and the product (30 g.) isolated by washing with water and distillation; b. p. 162°/1·5 mm., m. p. 25° (Found: N, 5·7. Calc. for $C_{17}H_{15}N$: N, 6·0%). (Schultz, Robb, and Sprague, *loc. cit.*, obtained this compound by the potassium *tert.*-butoxide method, and give b. p. 129—131°/1·5 mm.)

2 : 2-*Diphenylpent*-4-*en*-1-*carboxyamide*.—The above cyanide (2 g.), potassium hydroxide (4 g.), water (2 c.c.), and ethylene glycol (20 c.c.) were boiled for 20 hours. Traces of ammonia were evolved, and a neutral product (0·75 g., m. p. 130—135°) was obtained on cooling. Recrystallisation from benzene–petroleum (b. p. 60—80°) afforded glistening white flakes of the *amide*, m. p. 163—164° (Found: N, 5·8. $C_{17}H_{17}ON$ requires N, 5·6%).

αα-*Diphenyl*-γ-*valerolactone from* 1-*Cyano*-1 : 1-*diphenylbut*-2-*ene*.—The cyanide (2·3 g.) and 80% (by weight) sulphuric acid (10 g.) were heated at 185° for 1½ hours. Water (10 c.c.) and alcohol (5 c.c.) were added, and the mixture refluxed for 30 minutes. On cooling, αα-diphenyl-γ-valerolactone (1·2 g., m. p. 105—109°) separated; recrystallisation from petroleum (b. p. 80—100°) gave the pure lactone, m. p. 112·5—115°, not depressed on mixing with a specimen prepared by hydrolysis of the imino-compound.

Hydrolysis of αα-*Diphenyl*-γ-*valerolactone*.—The lactone (1·0 g.), potassium hydroxide (4·0 g.), water (10 c.c.), and alcohol (5 c.c.) were boiled for 3 hours. The solution was diluted, cooled, and carefully acidified with acetic acid (4 c.c.). The solid acid (1·07 g.; m. p. 94—96°) formed small needles, m. p. 95—95·5°, from ethyl acetate–petroleum (b. p. 40—60°). Prolonged heating during the m. p. determination, or even drying for analysis in a desiccator, regenerated the original lactone, m. p. and mixed m. p. 114·5—116°.

2-*Hydroxy*-3 : 3-*diphenyl*-5-*methyl*-2-*ethyltetrahydrofuran*.—αα-Diphenyl-γ-valerolactone (5·0 g.) in dry benzene (50 c.c.) was refluxed for 18 hours (dry nitrogen atmosphere) with an excess of Grignard reagent prepared from ethyl bromide (8·8 g.), magnesium (2·0 g.), and ether (75 c.c.). The ether solution was treated with dilute hydrochloric acid, washed with water, and dried (Na_2SO_4). Distillation of the ether and trituration with petroleum (b. p. 40—60°) afforded a solid (4·9 g.; m. p. 121—122°). The *hydroxy*-compound formed fluffy white needles, m. p. 124·5—125° after three crystallisations from benzene–petroleum (b. p. 60—80°) (Found: C, 80·15; H, 8·3. $C_{19}H_{22}O_2$ requires C, 80·9; H, 7·8%). The compound was stable to boiling aqueous-alcoholic sodium hydroxide, and no ketonic derivatives were obtained with alcoholic solutions of semicarbazide or 2 : 4-dinitrophenylhydrazine sulphate.

2-*Acetoxy*-3 : 3-*diphenyl*-5-*methyl*-2-*ethyltetrahydrofuran*.—The hydroxy-compound (1·0 g.), pyridine (6 c.c.), and acetic anhydride (0·7 c.c.) were heated at 100° for 6 hours. Decomposition with water and extraction with ether–benzene afforded the *acetate* (0·4 g.; m. p. 110—111°, b. p. 170—175°/5 mm.), crystallising from petroleum in white needles, m. p. 111—112·5° (Found: C, 77·5; H, 7·9. $C_{19}H_{20}O_2$ requires C, 77·8; H, 7·4%). Boiling with aqueous-alcoholic sodium hydroxide regenerated the original hydroxy-compound, m. p. and mixed m. p. 124—125°.

3 : 3-*Diphenyl*-5-*methyl*-2-*ethylidenetetrahydrofuran*.—The hydroxy-compound (1·0 g.) was boiled for 2 hours with methanol (50 c.c.) containing dry hydrogen chloride (1·0 g.). Removal of the solvent and trituration with water gave a solid, which was recrystallised from aqueous methanol. The *ethylidene* compound was obtained in large white prisms, m. p. 90—91° (Found: C, 86·0; H, 8·0; OMe, 0·4. $C_{19}H_{20}O$ requires C, 86·4; H, 7·6; OMe, 0·0%). The same substance was obtained with ethyl-alcoholic hydrogen chloride.

The author is indebted to Drs. W. F. Short and D. A. Peak for valuable advice.—Research Laboratories, Messrs. Boots Pure Drug Co. Ltd., Nottingham. [*Received, January 27th*, 1948.]

The Preparation of N-(2 : 4-*Dinitrophenyl*)- *and of* N-(2 : 6-*Dinitrophenyl*)-*phthalimide.* By Herbert H. Hodgson and Douglas P. Dodgson.

During attempts to obtain a better isolation of the 20—25% yield of the 1-chloro-2 : 6-dinitrobenzene which is formed during the mononitration of *o*-chloronitrobenzene, the crude nitration product (Hodgson and Dodgson, this vol., p. 1006) was fused for 30 minutes at 120° with potassium phthalimide. A readily crystallisable compound of m. p. 195—196° was obtained from the reaction complex, which, however, did not correspond with any of the simple possible reaction products anticipated, *viz.*, the *N*-(2 : 4- and 2 : 6-dinitrophenyl)phthalimides and the *N*-(2 : 4 : 6-trinitrophenyl)phthalimide previously made by Schmidt (*Ber.*, 1889, **22**, 3249), and has so far not been identified. The above *N*-dinitrophenylphthalimides, however, have not been previously reported and are now described. Attempts to prepare *N*-(2 : 4-dinitrophenyl)phthalanilic acid by the method of Sherrill, Schaeffer, and Shoyer (*J. Amer. Chem. Soc.*, 1928, **50**, 474), whereby 2 : 4-dinitroaniline is refluxed with phthalic anhydride in chloroform solution, showed that no reaction had occurred even after 9 hours.

N-(2 : 4-*Dinitrophenyl*)*phthalimide* was obtained when 2 : 4-dinitroaniline (1·8 g.) was heated with phthalic anhydride (1·5 g.) for 5 hours at 260°. After cooling, the powdered mass was triturated with cold N-sodium hydroxide, and the solid *N*-(2 : 4-dinitrophenyl)phthalimide filtered off; it crystallised from glacial acetic acid (charcoal) in cream-yellow plates, m. p. 192° (Found : N, 13·6. $C_{14}H_7O_6N_3$ requires N, 13·4%).

N-(2 : 6-*Dinitrophenyl*)*phthalimide*, prepared in like manner from 2 : 6-dinitroaniline (1·8 g.) and phthalic anhydride (1·5 g.), crystallised from glacial acetic acid (charcoal) in lemon-yellow prisms, m. p. 202° (Found : N, 13·6. $C_{14}H_7O_6N_3$ requires N, 13·4%).

The authors desire to thank the Huddersfield Education Authority for a Research Scholarship to one of them (D. P. D.), Imperial Chemical Industries, Ltd., Dyestuffs Division, for gifts of chemicals, and Mr. Frank Hobson for the microanalyses.—Technical College, Huddersfield. [*Received, January 26th*, 1948.]

OBITUARY NOTICE.

PERCY FARADAY FRANKLAND.*

1858—1946.

PERCY FARADAY FRANKLAND was born in London on October 3rd, 1858. He was the second son of Sir Edward Frankland, whose contributions to chemical thought in the nineteenth century, and whose researches on the purification of water, have established his reputation as one of the most outstanding scientists of the period.

Edward Frankland, who was resident in London, succeeded Hofmann as Professor of Chemistry at the Royal School of Mines in 1865, and his son thus had the opportunity of becoming acquainted with many of the famous scientific personalities of the day, including, when he was very young, Faraday, who was his godfather. When a boy he was taken by his father to the Scottish Highlands (in 1867 and 1870), as well as to the English Lake District. He also stayed frequently with his grandparents at Leyland in Lancashire. Perhaps in this way he developed a great liking for the North, and more especially for its wilder scenery.

Percy Frankland was a pupil at University College School from 1869 to 1874, and in 1875 proceeded to the Royal School of Mines. He was a student under Edward Frankland, Guthrie, Huxley, Judd, and Warington Smyth, at a period when the science establishments of the Royal School of Mines were being transferred to South Kensington. Until 1881, there was no Associateship course in subjects other than mining, metallurgy, and geology in the Royal School of Mines, and Frankland took the Associateship (A.R.S.M.) in geology, which included, however, a considerable amount of chemistry, as well as biology, physics, and applied mechanics. It appears that students taking the Associateship course used to oscillate between Jermyn Street and South Kensington in attendance at the science laboratories. Frankland gained the A.R.S.M. diploma in geology and the Forbes Prize. He was awarded a Brackenbury entrance scholarship at St. Bartholomew's Hospital in 1878, and graduated B.Sc. of the University of London in 1881. As a young man he was keenly desirous of entering the medical profession, but parental persuasion induced him to take up chemistry, although his interest in biology persisted throughout his life.

He spent two years at the University of Würzburg, where he came under the influence of Wislicenus, under whom he graduated Ph.D. with the distinction *summa cum laude*. The scientific interests which he acquired at Würzburg were to influence his choice of a field for research. There is, in fact, a line of continuity from the researches of Sir Edward Frankland, through Wislicenus, to those of Percy Faraday Frankland. At Würzburg he had astonished the Germans by riding a " penny farthing " high bicycle, and his affection for cycling continued throughout a good deal of his life. He was a good linguist and spoke German like a native, his French was a dramatic *tour de force*, and he would enjoy declaiming a few appropriate phrases from Dante. He saw the Germans in occupation of France in 1871, and on that occasion saw Bismarck, Moltke, and von Roon. He was strongly impressed by the glamour of military operations, and, familiar with conscription in Germany, he advocated it in this country. On his return from Germany, he enlisted enthusiastically in the Artists' Rifles, commanded by Sir Frederick Leighton, who appeared on field days on a white charger.

On his return to London in 1880 from Würzburg, Frankland became a demonstrator of practical chemistry in charge of the north chemical laboratory at the Normal School of Science, South Kensington, under his father, Edward Frankland. He occupied a private room at the west end of the building, from which he supervised the laboratory training of the students. The courses at that time included no organic chemistry, but consisted of qualitative inorganic analysis during the first term, and gravimetric analysis, including a complete analysis of minerals and ores, during the second term of the course. Frankland, who was very interested in consulting practice, spent much time, in conjunction with his father, on the chemical analysis of water supplies, and himself developed their bacteriological investigation.

He married in 1882 Grace, youngest daughter of Joseph Toynbee, F.R.S., the celebrated aurist. He lived at Grove House, Pembridge Square, an old house, now demolished, which had formerly stood in a large garden in the open country. Here he set up the laboratory in which he conducted water analysis in conjunction with his father. His interest in biology was instrumental in enabling him to become a pioneer in bacteriology and in striking out from the purely chemical side of water analysis practised by his father. He contributed to the British

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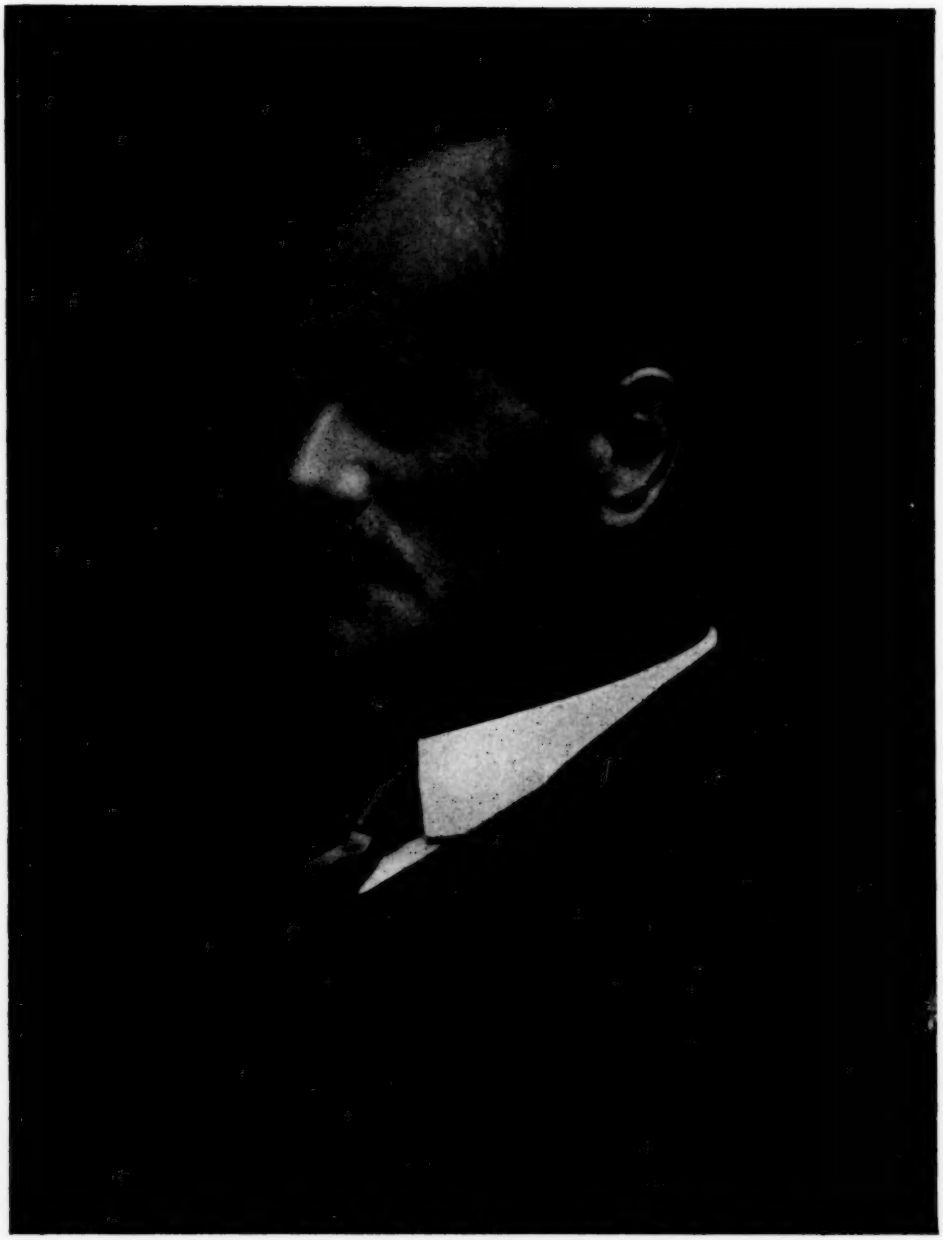

PERCY FARADAY FRANKLAND,
PRESIDENT, 1911—1913.

[*To face p.* 1996.

and foreign scientific journals on bacteriology and on the techniques for the analysis and the purification of water, and his discoveries proved to be of considerable value to the water companies in this country. In 1885 he was responsible for the inauguration of a monthly systematic bacteriological examination of London's water supplies.

On one occasion, a leaking bottle of ether led to an explosion which blew out the windows of his laboratory and even demolished the banisters of the staircase. His wife rushed upstairs and was relieved to find that he and his assistant were somewhat dazed, but unhurt. A crowd gathered outside, suspecting that the house was occupied by anarchists. It was probably this experience which led to his taking meticulous precautions against fire and explosions in his laboratories.

On his wedding tour he visited Westmorland and Yorkshire, and became much attached to Ravenstonedale, which was visited afterwards on several occasions. He and his wife returned in 1909 and purchased some farms, and from 1910 to 1914 they carried out farming during the university vacations, with a considerable measure of success. His country house and farm was Needlehouse, and it was mainly a sheep farm on the Fells. In the earlier days he and his wife did a good deal of cycling, and on one occasion they rode a " sociable " bicycle from London to Norwich, accompanied by a collie dog.

Frankland and his wife travelled extensively in Germany, Austria, Italy, Switzerland, Norway, and Sweden, and also visited Finland, Russia, Athens, Constantinople, and Ragusa. They paid long visits both in summer and winter to Norway and Sweden, where they made many friends and enjoyed the type of life and setting which they were afterwards able to reproduce to some extent in Westmorland among kindred people. He was a competent skater and took up ski-ing.

Frankland was keenly interested in history, both British and European, and had a considerable bias towards chemical history : he deplored the fact that the history of science was taught so inadequately. Although not a performer, he was keenly interested in music, his favourite composers being Mozart, Wagner, and Tschaikowsky, but he was not attracted by modern music or modern art. He was ahead of his time in his enjoyment of the rural scene and lonely places, as is obvious from his decision to settle in one of the most remote corners of Westmorland and his later retirement to Loch Awe.

After leaving London in 1888 to become Professor of Chemistry at Dundee, he lived at 2 Norwood Crescent, in that town, and took much pleasure in the romantic view from his windows across the Tay to the hills of Fife. He was a great friend of the late Professor Purdie of St. Andrews, and of Sir D'Arcy W. Thompson, then his colleague at Dundee. Purdie and Frankland were students together under Wislicenus, and they were the pioneers of stereochemistry in this country. Sir D'Arcy Thompson says of him in a letter to his son : " Your father was my colleague for a few years only, but he and your mother, too, made a far deeper impression on my life than many others with whom I worked for a much longer time. To tell you all that that impression meant is not possible to me, but the main thing is that I soon learned to look upon him as a man of singularly high principle, of unusual integrity and of simple goodness."

In a presidential address which Sir D'Arcy Thompson gave on the fiftieth anniversary of the foundation of the Dundee Social Union (in 1938), he spoke of the dreadful poverty of Dundee fifty years before : " Of all those young professors who had just come to the town, I doubt if there was one who was not shocked and saddened by the poverty which Dundee openly displayed. A certain professor came for a few years, and then left Dundee on promotion. He was a little better off than the rest of us, but far from a rich man; but he left a large sum of money to be spent quietly and without advertisement to help the poorest children of Dundee." The professor was, of course, Percy Frankland.

In the early history of University College, Dundee, the number of professors was small, and they were all men of exceptional gifts. Carnelley, the first Professor of Chemistry, came to Dundee at the foundation of the College in 1882, and was succeeded by Frankland in 1888. Frankland was liked as a good teacher who took pains to illustrate his lectures by experiments which always succeeded. Although his lectures were experimental, there was insistence on the necessity for a full understanding of the philosophic background of chemistry. He was considered by those who knew him to be one of the great teachers of the time. The subject of textile chemistry being of great importance at Dundee, he and his wife paid visits to various German technical institutes in a search for information of use to the industry.

At Dundee, his main scientific interest was in stereochemistry and in the preparation of pure cultures of bacilli, which were allowed to grow in solutions of sugars. In these latter researches he was much helped by his wife, and jointly with her, he published a volume on " Micro-

organisms in Water " (1894) and a life of Pasteur (1897). He also published in 1892 a popular book entitled " Our Secret Friends and Foes," which he dedicated " to the companion whose sympathy and invaluable assistance have so greatly enhanced the enjoyment of scientific work." Probably in few cases have husband and wife collaborated so effectively and enthusiastically in both research and professional work. On one occasion it was said, " Many women in the past have helped their husbands, but Percy Frankland is the first man who had the chivalry to admit it." The researches on the chemical reactions occurring during fermentation and his results on the chemistry of optically active compounds, which were recognized by the award of the Fellowship of the Royal Society in 1891, are referred to later.

On going to Birmingham in 1894 as Professor of what was then Mason College, where he succeeded Professor W. A. Tilden, he lived first in Edgbaston, where he took with great enthusiasm to the safety bicycle, and later at The Dell, Northfield, where he devoted much of his time to walking, riding, and driving in the attractive rural surroundings. His interest in cycling did not extend to motor-cycling or to the motor-car. He regarded high speeds on the road as criminal, and was very indignant at the high death-rate due to this cause.

He was an impetuous, generous, warm-hearted man, ever eager to combat injustice of any kind. This sometimes led to his frequent intervention in situations to which most people would have preferred to turn a blind eye. On one occasion he attempted to prevent the arrest of a small boy by a police officer for picking up apples under a hedge. Shortly after this exploit, which led to his appearance in the police court, he was made a J.P. on the Birmingham Bench, in which capacity he was greatly respected, devoting much thought and energy to his duties.

It was often assumed that Frankland would keep himself apart from the life of the students when he moved to Birmingham, but nothing was further from the truth. Under a superficial irascibility there lay a kindly disposition and a deep interest in his students, and his irascibility was invariably found to be occasioned by good reasons. He visited the teaching laboratories daily, and his manner was dignified and somewhat unbending. His experience in chemical analysis and gas analysis led him to take a deep interest in quantitative analysis. He was very insistent on scrupulous cleanliness and was very critical of any untidiness. He was very stimulating when the work was done well. Carelessness of experiment, speech, or thought made him very angry, sometimes violently so. He could not tolerate anything bogus or insincere.

Once his outer skin had been penetrated, the student realized that he had found a true friend who was always ready to give help to enable him to overcome difficulties. The penetration was frequently brought about by tennis or croquet parties at The Dell during week-ends. Soon after his appointment, the tempo of the work done in the department began to quicken. Students were not encouraged to continue a placid existence. They were encouraged to develop their talent for lecturing and participating in debate at the University of Birmingham Chemical Society, which society Frankland conducted with enthusiasm and success.

His lectures at Birmingham were very fully illustrated by experiments prepared with great care. He regarded them as very important, and his standard was very high. His lectures were not conversational or colloquial, but given in the somewhat old-fashioned correct lecture style. The lecture assistant was by far the most important member of the laboratory staff, and Frankland said on one occasion, " Always remember you can get a professor by sending a telegram or two, but not a lecture assistant."

By 1900 the number of students was large and the staff inadequate in numbers, so that the teaching duties were very heavy. Very thorough in his methods himself, he did not tolerate anything that looked like slackness on the part of his staff. Once seriously offended in this respect, he did not forget, and it was not easy afterwards to repair the mischief. As a chief, though outwardly severe in his demeanour, he was extremely helpful in discussing research problems with them and obtaining financial assistance for their researches.

He had an agreement with the University by which he could run a private water analysis laboratory in the department and employ staff for the purpose. He acted as consultant to many of the largest water companies in the kingdom.

The University of Birmingham owes much to Frankland's strong personality and his organizing ability as Dean of the Faculty of Science. He believed strongly in the value of research as part of the student's training for the first degree in science, and his influence was felt in the establishment in this country of science degrees for postgraduate research. He took a keen interest in chemistry as a profession and as a part of the national life. He was President of the Institute of Chemistry from 1906 to 1909, and was the first president to hold that office who had entered by the " iron gates of examination." This was particularly appropriate since

his father was the first President of the Institute. As President, he contributed very largely to the solution of the problems which confronted the chemical profession at that time. He was keenly interested in the code of ethics of professional men, and from his position as a university professor and also as a consultant he was able to legislate wisely on points of divergence between the two branches of the profession. He served as censor of the Institute from 1906 to 1921. At his suggestion, Council established its examination in biological chemistry, and he provided the funds for the special apparatus needed in the examination.

Frankland was President of the Chemical Society in 1912 and 1913, and his two presidential addresses review, amongst other topics, the definition of an asymmetric carbon atom, the quantitative connexion between the degree of molecular rotation and constitution, the question of *cis–trans* addition to unsaturated compounds, and the Walden inversion. His major writings were distinguished by their completeness and thoroughness. The length of the paper was a minor consideration. His lectures to the Chemical Society were models of clarity, and still have their value for their suggestiveness regarding stereochemical problems. He was always sure of a " full house," although his lectures were liable to extend over two hours rather than one. His Memorial Address to Pasteur (*J.*, 1897, **71**, 683) is an example of his literary powers and gift of fine writing. This lecture forms one of the classics of the series of memorial lectures of the Chemical Society and shows his deep insight into the problems of bacteriology and into the personality of one of the most striking figures of all time.

He introduced many students and members of his staff to an appreciation of the problems of chemical industry. In 1915 he addressed the Society of Chemical Industry in Birmingham on " the chemical industries of Germany," and stirred the imagination of the industry. He realized very early the importance of the part which would be played by science in the development of this country. At the end of his lecture he referred scathingly to the popular slogan of the time, " business as usual, that *vulgar* phrase."

As Professor of Chemistry in the University of Birmingham, he was largely responsible in 1909 for the internal arrangements of the chemistry laboratories at Edgbaston, designed by Aston Webb. The students entered the building before the contractors had left, and it is recollected by some students that chemical analysis was carried out for a time in one laboratory before the floor-boards were complete. Five years later he was to vacate these laboratories and return to the Mason College laboratories in Edmund Street, to make room for an emergency military hospital which took over all the buildings at Edgbaston until the end of the first world war. The laboratory buildings were mainly used as a store and a mortuary. In very cramped laboratory accommodation at Edmund Street, Frankland carried out much research from 1914 to 1918, for the Chemical Warfare Committee, on synthetic drugs, on high-explosives intermediates, and on river effluents from explosives factories. He was a member of the Admiralty Inventions Board, and the Anti-Gas and Chemical Warfare Committees. He was Deputy Inspector of High Explosives (Birmingham Area) and took entire charge of tar-testing in the Midlands. He was very much involved in researches on mustard gas, and, in conjunction with Sir William Pope, was responsible for the adoption by Churchill, then Minister of Munitions, of Guthrie's method—by which this substance was prepared from ethylene and sulphur chloride, a vastly easier process than that employed by the enemy. Investigators had been misled by the references to Guthrie's method being incorrect, owing to the change in the atomic weight of carbon from 6 to 12. In 1916, he paid an extended visit to the Western Front, and in 1917 was a member of a special mission sent to Italy to report on chemical technology in that country. For his war activities he was awarded the C.B.E. and by the Italian Government he was made an Officer of the Order of St. Maurice and St. Lazarus. He received honorary doctorates from the Universities of Birmingham, Dublin, St. Andrews, and Sheffield. He was awarded the Davy Medal of the Royal Society in 1919.

At the end of the first world war, he retired at the age of sixty. His laboratory required rehabilitation after being used as a hospital, his academic researches had been seriously interrupted, and he felt that the problems of post-war were those for a younger man. He lived after his retirement at the House of Letterawe, Loch Awe, Argyllshire, among surroundings that had always appealed to him, and entertained his friends who visited him there. His house lay under the shadow of Ben Cruachan, with Ben Lui in the distance, in a beautiful and romantic setting. Close by, on a small promontory, stood the ruins of Kilchurn Castle, formerly a stronghold of the red MacGregors against their hated foes, the black Campbells, in those grim days when the clansmen settled their disputes by resorting to the claymore and the *sgian dubh*. Farther to the south was the conspicuous memorial of the Gaelic poet, Duncan Ban MacIntyre.

Frankland was very fond of small boats and he learned to sail single-handed with the

assistance of books. He also had a motor-boat with an internally fixed motor, the *Circe*. This was like a life-boat, which would stand the sudden squalls and changes of wind very frequent on Loch Awe. He also had a small outboard motor-boat which he regarded as a fair-weather, light-load craft. He was delighted to take his friends by boat to see the beauty spots of Loch Awe, or by road to Inverary, Glencoe, or Ballachulish. In his retirement, even up to a few days before his death, he was always alive to the latest news from the political, scientific, and philosophical worlds, and followed the careers of his old students with great interest. Although the Franklands did not " have the Gaelic," they were very well liked by the Highlanders of the district for their easy friendliness, generosity and kindness. He survived the death of his wife only a few weeks, and they were buried together in the churchyard of Glenorchy. He leaves one son, Dr. Edward Frankland.

Research.

Frankland's research is characterised by its accuracy, and although most of his work was done in collaboration he was very careful to satisfy himself that the results were accurate, as far as he could tell. If anything was doubtful, it was checked again and again before it was accepted as a fact. He mistrusted the use of four-figure logarithms and the slide-rule by his students, and checked their work by arithmetical methods. He wrote to Professor McKenzie in 1939, " It has seemed to me for some time past that chemists are much less concerned about the accuracy of their results than they formerly were. In the old days, the publication of a result which proved to be erroneous was almost enough to shipwreck his career, and would, in any case, render all his subsequent work suspect. Indeed, a few errors of this kind would be sufficient to cast doubt upon a man's character for common honesty."

There was one occasion when Frankland described the optically active methyl and ethyl lactates prepared by the direct action of acid on alcohol, but his values for the rotatory powers were considerably lower than those of Purdie, who had prepared his esters by the interaction of alkyl halide and optically active silver lactate. Purdie suggested that Frankland's method led to optically impure products, owing to partial racemisation. As a matter of fact, Purdie found later that it was his esters which were impure; they were contaminated with a small quantity of alkylated product. The mistake was fortunate, for it led to the method of alkylation by silver oxide and methyl iodide, which proved of such great value in the study of carbohydrates.

On another occasion Frankland resolved inactive glyceric acid by the action of *Bacillus ethaceticus*, obtaining for barium L-glycerate a rotation $[\alpha]_D - 10{\cdot}01°$ in aqueous solution. Neuberg prepared the barium salt from D-glucuronic acid, obtaining $+ 17{\cdot}1°$ and resolved DL-glyceric acid with brucine to get barium salt with $- 17{\cdot}38°$. Neuberg suggested that the biological method of resolving acids is rather unsatisfactory. Accordingly, Frankland and Done (*J.*, 1905, **87**, 618) made a careful revision of the whole question and repeated the earlier results. Finally, Neuberg corrected his error, which was due to faulty polarimetric readings.

Frankland's earliest research was carried out in Wislicenus's laboratory in Würzburg on the interaction of diazonaphthalene with salicylic acid (*J.*, 1880, **37**, 746). The object of the investigation was to determine the place of entry of the diazo-group into salicylic acid, the group being introduced in the form of diazonaphthalene. The diazo-group was found to be attached in the *para*-position to the hydroxyl group, as is the case for most other substitutions into salicylic acid.

On his return to London, he became very much interested in consulting practice, in the methods of analysis of inorganic substances, and in the bacteriological examination of water. Frankland's interest in analysis is shown by the publication of a book on agricultural chemical analysis in 1883. He was also interested in gas analysis, and made a systematic investigation in 1884 of the coal gas supplied to consumers in the large towns in Great Britain and compared the analyses with those obtained by his father in 1851 (*J.*, 1884, **45**, 189). He noted that there had been a striking increase in the nitrogen content of coal gas due to the replacement of iron retorts in the manufacturing process by the more porous fireclay retorts.

His father, Edward Frankland, as a climber in Switzerland, had made the pioneer investigation of the diminution of the illuminating power of a flame with increasing altitude. In 1878 with Thorne (*J.*, **33**, 89) he had studied the luminosity of benzol when burnt with non-luminous combustible gases. In 1884—1885, the son published a series of papers on the illuminating power of gases which extended the work of his father (*J.*, 1884, **45**, 30, 227; *J. Soc. Chem. Ind.*, 1884, **3**, 271; *J.*, 1885, **47**, 235; *J. Soc. Chem. Ind.*, 1885, **4**, 387). He found that benzene was three times as effective as ethylene in increasing the illuminating power of coal gas, and that for ethane and propane the illuminating power is directly proportional to the number of carbon atoms in the molecule.

In 1885 he commenced an extensive series of investigations into the bacteriology of air and water (*Proc. Roy. Soc.*, 1885, **38**, 379; 1886, **40**, 509, 526; 1887, **42**, 267; 1889, **45**, 292; *J. Soc. Chem. Ind.*, 1885, **4**, 698; 1887, **6**, 316). These included the study of the methods of filtration of bacteria from water by greensand, coke, animal charcoal, and spongy iron, and the duration of the efficiency of such materials when employed as filters. He also modified the existing methods for extracting bacteria from the air (*Phil. Trans.*, 1887, *B*, **178**, 113). Instead of aspirating air slowly through wide glass tubes coated inside with nutrient gelatine, as was the current practice, Frankland aspirated air rapidly through a plug of glass wool which was afterwards shaken up and disintegrated in a flask containing melted gelatine. The flask was rotated until the medium solidified in a film, and was then incubated till the bacterial colonies developed and could be counted. This method was employed for the investigation of the numbers of bacteria in the air of towns, in the open, and inside buildings. A study was also made of the effect of common gases on the rate of growth of organisms (*Proc. Roy. Soc.*, 1889, **45**, 292).

In conjunction with his wife, in 1887 he determined the characteristics of a large number of bacteria obtained from the air, water, and soil, which had not been previously described, and studied their behaviour in dilute nitrate solutions (*Phil. Trans.*, 1887, *B*, **178**, 257; *Proc. Roy. Soc.*, 1888, **43**, 414; *J.*, 1888, **53**, 373). In 1890 they isolated nitrifying bacteria from the soil (*Phil. Trans.*, 1890, *B*, **181**, 107), and showed that they could be cultivated in ammoniacal solutions, the growth being accompanied by the gradual transformation of ammoniacal into nitrous nitrogen. He was invited to address many scientific societies, both at home and abroad, on the bacteriology of water. He also gave many popular lectures, and these and his books were important in bringing home to the general public the importance of this knowledge in the life of the community.

In association with Professor Marshall Ward, he was responsible for four reports to the Research Committee of the Royal Society on " The vitality of pathogenic organisms in water " (*Proc. Roy. Soc.*, 1892, **51**, 183; 1893, **53**, 164, 177; 1894, **56**, 315, 395, 549; 1896, **59**, 265). The persistence of anthrax bacillus, typhoid bacillus, and *B. coli communis* was studied under a wide variety of conditions in Thames water and Loch Katrine water. It was shown that the waters, after infection, were potentially dangerous over a long period of time.

Frankland was one of the first after Pasteur to study the chemical reactions in fermentation processes and to apply these to the isolation of pure substances. In this work he owed much to the assistance of his wife. His investigations on fermentation were mostly accomplished while at University College, Dundee, from 1888 to 1894.

He succeeded in obtaining optically active glyceric acid and sarcolactic acids by Pasteur's biochemical method of resolution. At that time glyceric acid was only known as a substance devoid of action on polarized light. In the fermentation of inactive calcium glycerate by *B. ethaceticus* he showed that approximately one half of the glycerate was not attacked by the bacillus (*J.*, 1891, **59**, 81, 96), and he was able to isolate the calcium salt of pure lævorotatory glyceric acid from this residue. The crystallographic and optical properties of crystals of the calcium salt were investigated by Tutton (*J.*, 1891, **59**, 233), and the crystal faces were found to show hemihedrism, which is usually associated with crystals of optically active substances. This investigation is similar to that on racemic tartaric acid by Pasteur, who was of the opinion that in the resolution of this acid accomplished by biochemical agency, the dextrorotatory acid was destroyed, leaving the lævorotatory acid unchanged. Following the preparation of this active glyceric acid, Frankland commenced an extended and very accurate investigation of the properties of esters of glyceric acid and its derivatives, which was of very great value in elucidating relationships between optical rotatory power and chemical constitution.

Frankland drew attention to changes in the activity of bacteria caused by their employment on unaccustomed tasks. A decrease in activity occurred if they were employed to ferment substances which were attacked with difficulty, but the activity was restored if they were allowed to act on easily fermented substances. He used mainly *B. ethaceticus*, *B. ethacetsuccinicus*, and *Pneumococcus friedlander* in his investigations on the chemical changes occurring during fermentation, and their action was shown to be highly specific (*Proc. Roy. Soc.*, 1890, **46**, 345; *J.*, 1891, **59**, 253; 1892, **61**, 254, 432, 737; 1893, **63**, 1028). The first two bacilli were first isolated by him. *B. ethaceticus* attacks glucose, cane sugar, milk sugar, and calcium glycerate, but there is no action on dulcitol, erythritol, glycol, calcium lactate, tartrate, citrate, and glycollate.

By the then available methods he carried out very detailed and accurate analyses of the chemical products from the fermentations. This followed on earlier investigations (*J.*, 1883, **43**, 294) in which he had studied the gases evolved from dry and moist grass and had shown that

the processes involved were probably those due to lactic fermentation. He concluded that the products were ethyl alcohol, acetic acid, some formic and succinic acids, carbon dioxide, and hydrogen. The formic acid was produced to the greatest extent when the fermentation was carried out in the absence of air. In the presence of air there was more carbon dioxide and hydrogen. From the carbon, oxygen, and hydrogen balance sheets of the reactions, it was concluded that some of the carbon dioxide and the whole of the hydrogen were derived from formic acid. After deducting the carbon dioxide liberated by acids from the calcium carbonate present in the medium, it was found that carbon dioxide and hydrogen were produced in equimolecular proportions in the gaseous products.

There were differences in degree between the products obtained from the fermentation of different pure substances. Thus, mannitol and dulcitol, fermented with *B. ethacetsuccinicus*, did not yield the final products in the same proportions (*J.*, 1892, **61**, 254). The same decomposition products were obtained with six, five, and three carbon-atom carbohydrates and polyhydric alcohols, but the proportions of acetic acid to ethyl alcohol varied.

His chemical researches on fermentation ceased in 1893, although he retained a considerable interest in bacteriology, as was shown by his papers on this subject and by his address to the Society of Chemical Industry in 1911, when he lectured on the bacteriological purity of water (*J. Soc. Chem. Ind.*, 1911, **30**, 319). He had, however, found another line of research that offered greater prospects of getting to grips with the problems of stereochemistry in which he became interested while under the teaching of Wislicenus.

A research on the optical rotations of the salts of glyceric acid in aqueous solution (*J.*, 1893, **63**, 296) was important in that it demonstrated that the relationships between optical activity and chemical constitution could not be interpreted in terms of existing theories. The results did not conform with Ostwald's dictum that the molecular rotation of salts in dilute solution should be independent of the inactive part of the molecule, nor were they in accord with the suggestion made by Crum Brown and Guye independently that the molecular dissymmetry was determined by the product of asymmetry.

In his stereochemical studies Frankland employed mainly derivatives of the optically active glyceric, tartaric, lactic, and malic acids. One series of derivatives was prepared by substitution of acetyl, benzoyl, toluoyl, chloroacetyl, pyromucyl, nitrobenzoyl, and methoxypropionoyl groups in place of the hydrogen atom in the hydroxyl groups of the acids. Both mono- and di-substituted acids were employed, although mainly the latter. In another series, similar groups were introduced into the amido-group, starting with tartramide. These compounds gave a very wide variety of groups around the asymmetric carbon atom, with very different masses and very different chemically.

The study of the quantitative connexion between the degree of molecular rotation and constitution received its initial impulse from the theory proposed by Crum Brown and Guye that the *product of asymmetry* is a measure of the dissymmetry of the molecule as a whole. In this theory, P is the product of asymmetry which can be calculated, assuming that the four different masses (a, b, c, d) attached to the asymmetric carbon atom are concentrated at the apices of the tetrahedron, by the formula :

$$P = \frac{(a-b)(a-c)(a-d)(b-c)(b-d)(c-d)}{(a+b+c+d)^6}\,(l \sin \alpha)^6.$$

From an examination of the existing data it was concluded by Guye and Crum Brown that P was proportional to the molecular rotatory power. This theory was found by Frankland to be quite incapable of accounting even qualitatively for the facts of optical activity.

Frankland used the conception of the product of asymmetry as a basis for his earlier investigations, and he devised tests of its applicability. These tests consisted in modifying the masses of the groups around the asymmetric carbon atom and observing the effect on the molecular rotation and molecular volume. Also, by the use of isomeric substituents, such as the *ortho-*, *para-*, and *meta*-benzene derivatives, he examined the effect of altering the centre of gravity and moment of mass of the substituent group. He studied also the introduction of double and triple bonds and conjugated double bonds and cyclic groups into constituents placed around the asymmetric atom. Measurements of molecular volume were made at the same time as those on molecular rotatory power, and these were compared with those calculated by Traube's method, in order to be able to assess what degree of abnormality in the rotation was caused by association of the molecules. Also, the rotation was measured over a wide range of temperature, and the temperature coefficients were sometimes anomalous and had to be taken into account in the interpretation of the results.

NEW REAGENTS

8-HYDROXYQUINALDINE

a gravimetric reagent similar in application to 8-hydroxyquinoline but which does not react with aluminium.

See Merritt and Walker, Ind. Eng. Chem. (Anal.), 16, 387 (1944).

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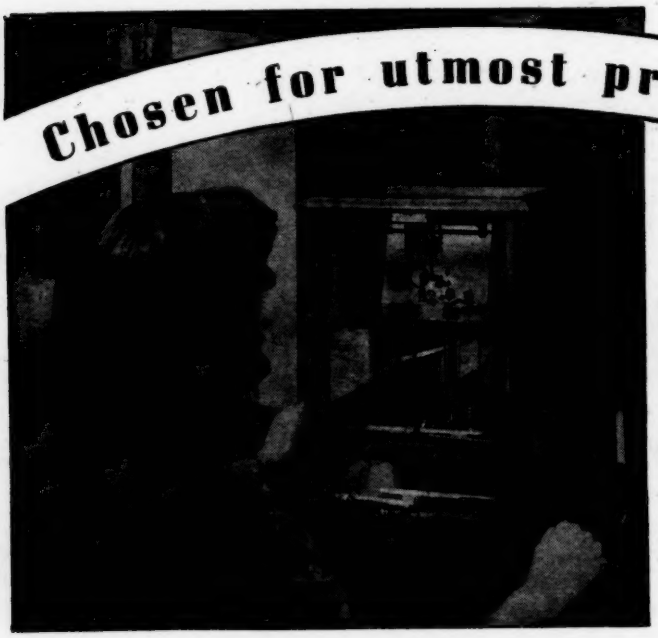

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